ETS
ISSUE BINDER

ETS AND
LUNG CANCER
IN NONSMOKERS

VOLUME I

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ETS AND
LUNG CANCER IN NONSMOKERS

VOLUME I

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THIS ISSUE BINDER IS INTENDED TO PROVIDE A BASIC, COMPREHENSIVE REVIEW OF THE SCIENTIFIC LITERATURE REGARDING A SPECIFIC TOPIC ON ETS AND THE HEALTH OF NONSMOKERS.

PRIMARY STUDIES AND REVIEWS HAVE BEEN HIGHLIGHTED TO IDENTIFY (1) USEFUL OR HELPFUL INFORMATION (YELLOW HIGHLIGHT) AND (2) ADVERSE RESULTS OR OPINIONS (BLUE HIGHLIGHT).

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PRIMARY EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

Currently, 29 epidemiologic studies examining lung cancer incidence and spousal smoking have been published.[1-29] Tables 1, 2 and 3 list the United States, Asian and European studies, respectively. For purposes of comparison, the relative risks (point estimates) given in the tables are the overall point estimates for spousal smoking reported in the papers. In some cases, the risk in the table was selected from numerous point estimates presented in the paper, based on different definitions of exposure, break-down of the sample by histological type, etc.

Brief synopses and copies of the papers associated with these studies follow this introduction, at Tabs 1 to 29, arranged in chronological order. The copies are highlighted in yellow for useful information and in blue for negative statements.

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United States Studies

Ten of these studies on spousal smoking and lung cancer in nonsmokers (one cohort, nine case-control) were conducted in the United States (Table 1).[3,5,7-9,11,14,16,24,25] **None of the relative risks (RR) for spousal smoking reported in these studies is statistically significant.** The most recently published paper, that by Janerich, et al., is based upon an unpublished dissertation by Luis Varela.[24] The Janerich, et al., paper discusses a subset of Varela's case-control study, and reports no statistically significant increased risk for spousal smoking, workplace exposure, or exposure in social settings. (It does, however, report a statistically significant increased risk for exposure during childhood (see below).) Overall, the Varela study is important because of its large size and appropriate study design.

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Table 1. United States Studies of Spousal Smoking in Women

Study	Risk Estimate(s)	Comment
Garfinkel, 1981	1.27 (95% CI 0.85-1.89) 1.10 (95% CI 0.77-1.61)	Large cohort study; results contrast with Hirayama
Correa, et al., 1983	2.07 (no CI; n.s.)	Extremely small sample size
Buffler, et al., 1984	0.78 (95% CI 0.34-1.81)	
Kabat and Wynder, 1984	not given	No significant differences between cases and controls regarding ETS exposure at home
Garfinkel, et al., 1985	1.23 (95% CI 0.94-1.60)	Numerous odds ratios presented
Wu, et al., 1985	1.2 (95% CI 0.5-3.3)	Adenocarcinoma only
Brownson, et al., 1987	1.68 (95% CI 0.39-2.97)	Hours per day as exposure category; adenocarcinoma only
Humble, et al., 1987	1.8 (95% CI 0.6-5.4)	
Varela, 1987	numerous	No statistically significant point estimate was presented in 73 different measures of spousal smoking
Janerich, et al., 1990	0.93 (95% CI 0.55-1.57)	Published data for subset of Varela, 1987
Kabat, 1990	0.90 (95% CI 0.46-1.76)	Study in progress; surrogate is "exposed in adulthood at home"

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Asian Studies

In contrast, 13 epidemiologic studies on spousal smoking and lung cancer in nonsmokers (one cohort, twelve case-control) have been conducted in China and Japan (hereafter, "Asian studies") (Table 2).[1,4,10,12,15,17,18,20-22,27,28,29] Of this group, several studies report statistically significant relative risks. However, none of the reported relative risks is greater than 2.5; relative risks under 3.0 have been described as "weak" (see Criticisms section in this notebook). Of particular interest is the 1990 paper by Wu-Williams, et al., conducted in northeastern China.[28] This paper reports a statistically significant negative risk associated with ETS exposure. Other factors (particularly indoor air quality) were reported to be associated with an elevated risk of lung cancer in the Wu-Williams, et al., study; such confounders were not always accounted for in the other Asian studies (see section on Confounders in this notebook).

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Table 2. Asian Studies of Spousal Smoking in Women

Study	Point Estimate(s)	Comment
Hirayama, 1981	2.08 (no CI)	Large cohort study; heavily criticized for improper age-standardization and other flaws
Hirayama, 1984	1.45 (90% CI 1.04-2.02)	Further report on above study
Chan and Fung, 1982	not given	Negative association; suggests more "passive smokers" among controls than cases
Lam, W.K., 1985	not given	Unpublished dissertation; suggests that spousal smoking may be associated with peripheral adenocarcinoma
Akiba, et al., 1986	1.5 (90% CI 1.0-2.5)	Study of atom bomb survivors
Gao, et al., 1987	0.9 (95% CI 0.6-1.4)	"Overall exposure" as surrogate
Koo, et al., 1987	1.64 (95% CI 0.87-3.09)	
Lam, T.H., et al., 1987	1.65 (95% CI 1.16-2.35)	
Geng, et al., 1988	2.16 (95% CI 1.03-4.53)	
Inoue and Hirayama, 1988	2.25 (95% CI 0.91-7.10)	Very small sample size
Shimizu, et al., 1988	1.1 (no CI; n.s.)	Reported statistically significant elevated risks for smoking by case's mother or case's husband's father

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Study	Point Estimate(s)	Comment
Sobue, et al., 1990	0.94 (95% CI 0.62-1.40)	
Wu-Williams, et al., 1990	0.7 (95% CI 0.6-0.9)	Point estimate is statistically significantly negative
Liu, et al., 1991	0.77 (95% CI 0.30-1.96)	Presence of at least one smoker in household used as surrogate

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European Studies

Six studies on spousal smoking and nonsmoker lung cancer were conducted in Europe (Table 3).[2,7,13,19,23,26] Statistical significance was reported in two studies, both by the same research group.[2,26] No major cohort study has yet been conducted in Europe. The cohort studied by Gillis, et al., and Hole, et al., although large, has few lung cancer deaths.[7]

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Table 3. European Studies of Spousal Smoking in Women

Study	Risk Estimate	Comment
Trichopoulos, et al., 1981	2.4 (no CI)	Greece; small case-control study; has been heavily criticized
Trichopoulos, et al., 1983	2.4 (no CI) 3.4 (no CI)	Additional cases and controls added since first paper
Gillis, et al., 1984	not given	Scotland; cohort study; very few lung cancer death (4 cases, 4 controls in women)
Hole, et al., 1989	2.41 (95% CI 0.45-12.83)	Continuation of Gillis, et al., 1984
Lee, et al., 1986	1.00 (95% CI 0.37-2.71)	England
Pershagen, et al., 1987	1.2 (95% CI 0.7-2.1)	Sweden
Svensson, et al., 1989	1.2 (95% CI 0.4-2.9)	Sweden; surrogate is "exposure as adult at home or at work"
Kalandidi, et al., 1990	1.92 (95% CI 1.02-3.59)	Greece; related to Trichopoulos study

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Childhood Exposure to ETS and Adult Lung Cancer in Nonsmokers

When the Janerich, et al., paper was published in 1990, the media focused on a single statistically significant risk ratio (OR) reported by the authors, i.e., an estimated OR of 2.07 (95% CI 1.16-3.68) for "household exposure to 25 or more smoker-years during childhood and adolescence."[24] This OR is the only statistically significant estimate out of 13 exposure categories in the paper. A single statistically significant point estimate could have easily occurred by chance alone in a set of analyses this large.

Only a few other studies have included questions concerning exposure to ETS during childhood, i.e., parental smoking.[5,9,11,12,15,23,25,27] Regarding these studies, Ernst Wynder and Geoffrey Kabat wrote in a 1990 publication:

> No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

(Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.)

Table 4 presents the reported risk estimates from the studies (9 to-date) which discuss childhood ETS exposure and lung

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cancer in nonsmokers. The studies are arranged chronologically in the table. The abbreviation "n.s." stands for "not significant."

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Table 4. Childhood Exposure to ETS and Adult Nonsmoker Lung Cancer Risk

Study	Point Estimate	Statistical Significance
Correa, et al., 1983	not given	n.s.
Garfinkel, et al., 1985		
females	0.91 (95% CI 0.74-1.12)	n.s.
Wu, et al., 1985		
females	0.6 (95% CI 0.2-1.7)	n.s.
Akiba, et al., 1986	not given	n.s.
Gao, et al., 1987		
females	1.1 (95% CI 0.7-1.7)	n.s.
Svensson, et al., 1989		
females, father's smoking	0.9 (95% CI 0.4-2.3)	n.s.
females, mother's smoking	3.3 (95% CI 0.5-18.8)	n.s.
Janerich, et al., 1990		
1-24 smoker/yrs exposure	1.09 (95% CI 0.68-1.73)	n.s.
≥ 25 smoker/yrs exposure	2.07 (95% CI 1.16-3.68)	significantly positive
Kabat, et al., 1990		
males	0.73 (95% CI 0.34-1.59)	n.s.
females	1.68 (95% CI 0.86-3.27)	n.s.
Sobue, et al., 1990		
father's smoking	0.60 (95% CI 0.40-0.91)	significantly negative
mother's smoking	1.71 (95% CI 0.95-3.10)	n.s.
other household members	1.13 (95% CI 0.69-1.87)	n.s.

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Exposure to ETS in the Workplace and Lung Cancer in Nonsmokers

The issue of ETS in the workplace is currently a focus of public interest, as evidenced by the 1990 draft Guide to Workplace Smoking Policies prepared by the United States Environmental Protection Agency. This document is based on the EPA's draft risk assessment, which used data from epidemiologic studies which assessed ETS exposure in terms of spousal smoking, not smoking in the workplace.

The current epidemiologic data on workplace exposures to ETS and lung cancer in nonsmokers are reported in eleven studies which examined workplace exposure via questionnaire.[8,9,11,13,17,22-26,28] None of these studies provides adequate support for an increased risk of lung cancer associated with ETS exposure in the workplace. Only one study reports a single marginally statistically significant risk. The point estimates of the studies (in chronological order) are presented in Table 5. (In the table, "n.s." stands for "not significant.")

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Table 5. Exposure to ETS in the Workplace and Lung Cancer Risk in Nonsmokers

Study	Point Estimate	Statistical Significance
Kabat and Wynder, 1984		
males	18/25 cases vs. 11/25 controls	marginally significant
females	26/53 cases vs. 31/53 controls	n.s.
Garfinkel, et al., 1985		
females, 5 yr exposure	0.88 (95% CI 0.66-1.18)	n.s.
females, 25 yr exposure	0.93 (95% CI 0.73-1.18)	n.s.
Wu, et al., 1985		
females	1.3 (95% CI 0.5-3.3)	n.s.
Lee, et al., 1986	several indices	all n.s.
Koo, et al., 1987		
females	several ORs	all n.s.
Shimizu, et al., 1988		
females	1.2 (no CI given)	n.s.
Svensson, et al., 1989		
females, at home or at work	1.2 (95% CI 0.4-2.9)	n.s.
females, at home and at work	2.1 (95% CI 0.6-8.1)	n.s.
Janerich, et al., 1990		
150 person/yrs exposure	0.91 (95% CI 0.80-1.09)	n.s.
Varela, 1987	27 analyses	all n.s.
Kabat, 1990		
males	0.98 (95% CI 0.46-2.10)	n.s.
females	1.00 (95% CI 0.49-2.06)	n.s.

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Study	Point Estimate	Statistical Significance
Kalandidi, et al., 1990 females	1.08 (95% CI 0.24-4.87)	n.s.
Wu-Williams, et al., 1990 females	1.1 (95% CI 0.9-1.6)	n.s.

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Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer: A Study from Japan," British Medical Journal I, 282: 183-185, 1981.

As part of Hirayama's longitudinal record-linkage study, 91,540 non-smoking wives aged 40 and above in 29 Japanese health center districts were followed for 14 years (1966-79). Death certificates were used to assess cause of death.

Relative risks of 1.61 (for husband being an exsmoker or smoking 1-19 cigarettes/day) and 2.08 (for husband smoking 20 or more cigarettes/day) were presented without confidence intervals. The author claims that wives of heavy smokers had a higher risk of lung cancer and that his data support a dose-response relationship. He also claims that a similar pattern was evident when the data were analyzed by age and occupation of the husband, with higher risks in agricultural families with husbands aged 40-59. The inclusion of agricultural families was designed to address the possible effect of "urban factors" thought to influence lung cancer incidence.

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Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan

TAKESHI HIRAYAMA

Abstract

In a study in 29 health centre districts in Japan 91 540 non-smoking wives aged 40 and above were followed up for 14 years (1966-79), and standardised mortality rates for lung cancer were assessed according to the smoking habits of their husbands. Wives of heavy smokers were found to have a higher risk of developing lung cancer and a dose-response relation was observed. The relation between the husband's smoking and the wife's risk of developing lung cancer showed a similar pattern when analysed by age and occupation of the husband. The risk was particularly great in agricultural families when the husbands were aged 40-59 at enrolment. The husbands' smoking habit did not affect their wives' risk of dying from other disease such as stomach cancer, cervical cancer, and ischaemic heart disease. The risk of developing emphysema and asthma seemed to be higher in non-smoking wives of heavy smokers but the effect was not statistically significant.

The husband's drinking habit seemed to have no effect on any causes of death in their wives, including lung cancer.

These results indicate the possible importance of passive or indirect smoking as one of the causal factors of lung cancer. They also appear to explain the long-standing riddle of why many women develop lung cancer although they themselves are non-smokers. These results also cast doubt on the practice of assessing the relative risk of developing lung cancer in smokers by comparing them with non-smokers.

Introduction

The possible consequences to the health of non-smokers of long-term exposure to cigarette smoke (passive smoking) should be studied thoroughly because the side-stream and second-hand smoke of cigarettes contain various toxic substances, including carcinogens.[1 2] The need for such a study increased by the report of small-airways dysfunction in non-smokers chronically exposed to tobacco smoke.[3]

The effect of passive smoking on lung cancer was studied by following 91 540 non-smoking housewives aged 40 and above and measuring their risk of developing lung cancer according to the smoking habits of their husbands.

National Cancer Centre Research Institute, Tokyo
TAKESHI HIRAYAMA, MD, MPH, chief of epidemiology division

Methods

To study the consequences to health of such factors as cigarette smoking, alcohol drinking, occupation, and marital status, a prospective population study has been in progress in 29 health centre districts in six prefectures in Japan since the autumn of 1965. In total 265 118 adults (122 261 men and 142 857 women) aged 40 years and over, 91-99% of the census population, were interviewed and followed by establishing a record linkage system between the risk-factor records, a residence list obtained by special yearly census, and death certificates.

Since the effect of direct smoking of cigarettes in this study has already been reported,[4-7] my study focused on the effect of husband's smoking on the risk of lung cancer in their non-smoking wives. Such observation was possible since detailed questions about lifestyle, including smoking habits, were asked of husbands and wives independently at the start of this study. No subjective bias was therefore conceivable.

A total of 346 deaths from lung cancer in women were recorded during 14 years of follow-up (1966-79). Of these women 245 were married, and 174 of these were also non-smokers. These cases occurred among 91 540 non-smoking married women whose husbands' smoking habits were studied. The risk of lung cancer was carefully measured, taking into consideration possible confounding variables.

Results

Wives of heavy smokers were found to have a higher risk of developing lung cancer than wives of non-smokers and a statistically significant dose-response relationship was observed (Mantel-extension χ test result being 3·299; two-tailed $p = 0{\cdot}00097$). Age-occupation standardised annual mortality rates for lung cancer were 8·7/100 000 (32 out of 21 895) when husbands were non-smokers or occasional smokers,

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14·0 (86 out of 44 184) when husbands were ex-smokers or daily smokers of 1-19 cigarettes, and 18·1 (56 out of 25 146) when husbands were daily smokers of 20 or more cigarettes. These figures gave risk ratios of 1·00, 1·61, and 2·08 respectively. A similar trend was observed in age and occupation groups of husbands (table I).

TABLE I—*Standardised mortality for lung cancer in women by age, occupation, and smoking habit of the husband (patient herself a non-smoker)*

Husband's smoking habit:	Non-smoker	Ex-smoker or 1-19/day	≥20/day
Husband's age: 40-59 years			
Population of wives	14 020	30 676	20 584
No of deaths from lung cancer	11	40	36
Occupation-standardised mortality/100 000	5·64	9·34	13·14
Husband's age: ≥60 years			
Population of wives	7875	13 508	4877
No of deaths from lung cancer	21	46	20
Occupation-standardised mortality/100 000	15·79	24·44	29·60
Standardised risk ratio for all ages	1·00	1·61	2·08
Husband working in agriculture			
Population of wives	10 406	20 034	9391
No of deaths from lung cancer	17	52	24
Age-standardised mortality/100 000	9·54	17·02	18·40
Husband working elsewhere			
Population of wives	11 489	24 140	16 070
No of deaths from lung cancer	15	34	32
Age-standardised mortality/100 000	9·13	10·46	17·78
Standardised risk ratio for all occupations	1·00	1·43	1·90

The relation between the husband's smoking habit and the wife's risk of developing lung cancer was particularly significant in agricultural families when the husband was aged 40-59 at enrolment (Mantel-extension chi being 2·597 or two-tailed p = 0·0094); lung cancer risk ratios were 1·00, 3·17, and 4·57 when husbands were non-smokers or occasional smokers, ex-smokers or smokers of 1-19 cigarettes daily, and smokers of 20 or more cigarettes daily respectively (table II).

TABLE II—*Mortality for lung cancer in women by occupation and by smoking habit of husband among men aged 40-59 (patient herself a non-smoker)*

Husband's smoking habit:	Non-smoker	Ex-smoker or 1-19/day	≥20/day
Agricultural workers:			
Population of wives	5 999	12 753	7150
No of deaths from lung cancer	3	20	16
Mortality/100 000	3·48	11·93	15·92
Other workers			
Population of wives	8 021	17 923	13 434
No of deaths from lung cancer	8	20	20
Mortality/100 000	7·15	8·09	11·05
Standardised risk ratio for all occupations	1·00	1·67	2·36

The husbands' smoking habits seemed to have no effect on their wives' risk of developing other major cancers, such as cancers of the stomach (n = 716) and of the cervix (n = 250) or ischaemic heart disease (n = 406). The risk of developing emphysema and asthma seemed to be higher among the non-smoking wives of smokers, but the effect was not statistically significant (table III).

Other characteristics of the husbands, such as their alcohol drinking habits did not affect mortality from lung cancer in their wives. The relative risk ratios of death from lung cancer were 1·00, 1·13, and 1·18 (p = 0·396) respectively when husbands were non-drinkers, occasional or rare drinkers, and daily drinkers. Similar results were found with other causes of death (table IV).

Finally, the effect of passive smoking was compared with the effect of direct smoking. The effect of passive smoking was around one-half to one-third that of direct smoking. The relative risk of developing lung cancer by passive smoking was about 1·8 compared with about 3·8 in direct smokers (fig 1).

TABLE III—*Age-occupation standardised risk ratio for selected causes of death in women by smoking habit of the husband (patient herself a non-smoker)*

Cause of death	Husband's smoking habit: Non-smoker	Ex-smoker, or 1-19 day	≥20 day	p value
Lung cancer (n = 174)	1·00	1·61	2·08	0·001
Emphysema, asthma (n = 66)	1·00	1·29	1·49	0·474
Cancer of cervix (n = 250)	1·00	1·15	1·14	0·249
Stomach cancer (n = 716)	1·00	1·02	0·99	0·720
Ischaemic heart disease (n = 406)	1·00	0·97	1·03	0·393

TABLE IV—*Age-standardised risk ratio for selected causes of death in women by alcohol-drinking habit of the husband*

Cause of death	Husband's drinking habit: Non-drinker	Occasional or rare drinker	Daily drinker	p value
Lung cancer (n = 174)	1·00	1·13	1·18	0·396
Emphysema, asthma (n = 66)	1·00	0·92	1·39	0·292
Cancer of cervix (n = 250)	1·00	0·84	0·89	0·514
Stomach cancer (n = 716)	1·00	0·88	0·95	0·285
Ischaemic heart disease (n = 406)	1·00	1·09	0·93	0·567

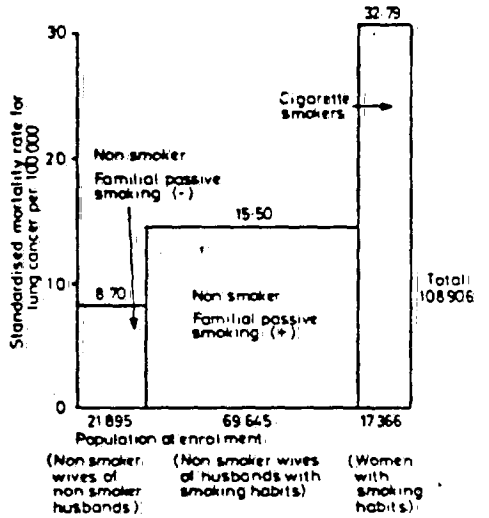

FIG 1—Lung cancer mortality in women according to the presence or absence of direct and familial indirect smoking.

Discussion

The possible effect of passive smoking was studied by following many non-smoking wives whose husbands had various smoking habits, and measuring their risk of developing lung cancer. Continued exposure to their husbands' smoking increased mortality from lung cancer in non-smokers up to twofold. The extent of the increase in the risk of developing cancer reached as high as 4·6 for non-smoking wives of agricultural workers aged 40-59 who smoked 20 or more cigarettes a day.

The fact that there was a statistically significant relation (two-tailed p = 0·00097) between the amount the husbands smoked and the mortality of their non-smoking wives from lung cancer suggests that these findings were not the result of chance. To determine whether such an effect was limited to lung cancer, similar studies were conducted with other causes of death. Although there seemed to be a relation between husbands' smoking habits and deaths from emphysema and asthma in their wives, the effect of passive smoking was strongest with

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lung cancer. Passive smoking did not seem to increase the risk of developing stomach cancer, cervical cancer, or ischaemic heart disease. We found that smoking was the only habit of the husbands to affect wives' mortality. The absence of an effect of husbands' drinking habits on mortality in their wives was shown as an example.

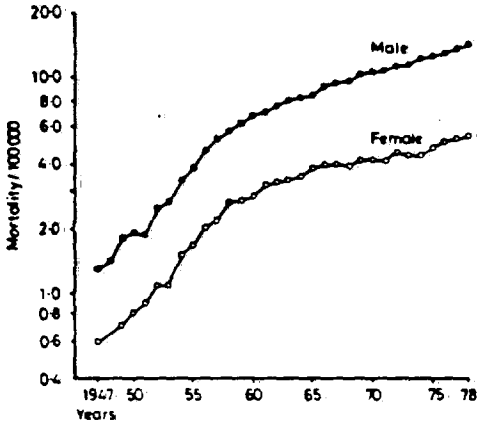

FIG 2—Age-adjusted mortality for lung cancer in Japan (1947-78).

The most important confounding variables would have been urban factors. Similar observations were therefore made for agricultural families and for non-agricultural families, and a similar dose-response relation was observed in both groups. The effect of passive smoking was most striking in younger couples in agricultural families, relative risk reaching 4·6, probably because of the lesser extent of the exposure to passive smoking outside the family in the case of rural residents. That the rate for non-smoking wives with husbands who were heavy smokers in urban families was lower than that in rural families is puzzling but probably reflects a longer period of mutual contact of couples in rural families. In urban families some couples meet only for a short period in the day.

Finally, the effects of passive smoking were compared with the effects direct smoking. The results clearly indicated that the effect of passive smoking is about one-half to one-third that of direct smoking in terms of mortality ratio or relative risk. In terms of attributable risk, however, the effect of passive smoking on lung cancer in women must be much more important than that of direct smoking (fig 1), especially in countries such as Japan where 73% of men but only 15% of women smoke. Therefore, although the relative risk of indirect smoking was smaller than that of direct smoking, the absolute excess deaths from lung cancer due to passive smoking must be important because of the large size of the exposed group.

The age-adjusted mortality rates for lung cancer have been sharply increasing both for men and for women in Japan (fig 2). As only a fraction of Japanese women with lung cancer smoke cigarettes, the reasons why their mortality from lung cancer parallels that in men have been unclear. The present study appears to explain at least a part of this long-standing riddle.

This observation also questions the validity of the conventional method of assessing the relative risk of developing lung cancer in smokers by comparing them with non-smokers. This study shows that non-smokers are not a homogenous group and should be subdivided according to the extent of previous exposure to indirect or passive smoking.

This work was supported by Grants-in-Aid for Cancer Research from the Ministry of Health and Welfare.

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(*Accepted 13 November 1980*)

ARSSMART. The hot Arssmart is called also Water-pepper, or Culrage. The mild Arssmart is called dead Arssmart Persicaria, or Peachwort, because the leaves are so like the leaves of a peach-tree; it is also called Plumbago.

The mild has broad leaves set at the great red joint of the stalks; with semicircular blackish marks on them, usually either blueish or whitish, with such like seed following. The root is long, with many strings thereat, perishing yearly; this has no sharp taste (as another sort has, which is quick and biting) but rather sour like sorrel, or else a little drying, or without taste. It grows in watery places, ditches, and the like, which for the most part are dry in summer. It flowers in June, and the seed is ripe in August.

As the virtue of both these is various, so is also their government; for that which is hot and biting, is under the dominion of Mars, but Saturn, challenges the other, as appears by that leaden coloured spot he hath placed upon the leaf.

It is of a cooling and drying quality and very effectual for putrified ulcers in man or beast, to kill worms, and cleanse the putrified places. The juice thereof dropped in, or otherwise applied, consumes all colds, swellings, and dissolveth the congealed blood of bruises by strokes, falls, etc. A piece of the root, or some of the seeds bruised, and held to an aching tooth, takes away the pain. The leaves bruised and laid to the joint that has a felon thereon, takes it away. The juice destroys worms in the ears, being dropped into them; if the hot Arssmart be strewed in a chamber, it will soon kill all the fleas; and the herb or juice of the cold Arssmart, put to a horse or other cattle's sores, will drive away the fly in the hottest time of Summer; a good handful of the hot biting Arssmart put under a horse's saddle, will make him travel the better, although he were half tired before. The mild Arssmart is good against all imposthumes and inflammations at the beginning, and to heal green wounds.

All authors chop the virtues of both sorts of Arssmart together, as men chop herbs for the pot, when both of them are of contrary qualities. The hot Arssmart grows not so high or tall as the mild doth, but has many leaves of the colour of peach leaves, very seldom or never spotted; in other particulars it is like the former, but may easily be known from it, if you will but be pleased to break a leaf of it cross your tongue, for the hot will make your tongue to smart, but the cold will not. If you see them both together, you may easily distinguish them, because the mild hath far broader leaves. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)

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Hirayama, T., "Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan," Preventive Medicine 13: 680-690, 1984.

This paper reports on the same population as Hirayama, 1981. In the population of 91,540 nonsmoking wives, 200 deaths from lung cancer were reported.

Hirayama calculated relative risks of 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were nonsmokers, ex-smokers, or smokers of 1-14, 15-19, or 20 or more cigarettes per day. Elevated risks of other cancers were also reported for nonsmoking women, based on the smoking of husbands: paranasal sinus cancer, brain tumors, and cancer of all sites excluding lung cancer.

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PREVENTIVE MEDICINE 13, 680–690 (1984)

Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan[1]

TAKESHI HIRAYAMA

National Cancer Center Research Institute, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan

Mortality of 91,540 nonsmoking wives was studied in relation to the smoking habits of their husbands by means of a cohort study in Japan. During 16 years of follow-up, 200 deaths from lung cancer took place. The relative risks of lung cancer in these nonsmoking wives were 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were nonsmokers, ex-smokers, or daily smokers of 1–14, 15–19, or 20 or more cigarettes daily, respectively. Corresponding relative risks for stomach cancer were 1.00, 1.16, 1.00, 1.00, and 1.01, respectively. Specificity of association and internal consistencies were observed. Among cancers of each site, a similar tendency toward risk elevation in nonsmoking wives with smoking husbands was observed for nasal sinus cancer, brain tumors, and cancer of all sites besides lung cancer. In interpreting these results, the significance of proximity in exposure to sidestream smoke in Japanese homes was stressed. © 1984 Academic Press, Inc.

INTRODUCTION

The possible health hazard due to passive smoking was evaluated by the observation of mortality in nonsmoking wives with smoking husbands. As reported previously (6), nonsmoking wives of heavy smokers had a significantly elevated risk of lung cancer. Results of our large-scale cohort study reported here not only confirm the results of the previous report, but also reveal additional evidence of the health consequences of passive smoking by pointing out excess deaths due to cancer of other selected sites.

MATERIALS AND METHODS

A prospective cohort study on the health consequences of cigarette smoking has been in progress in Japan since the fall of 1965. In total, 265,118 adults (122,261 men and 142,857 women) ages 40 years and above, 94.8% of the census population in the study area in 29 Health Center Districts in Japan, participated. They were interviewed from October 1 to December 31, 1965, and have been tracked by establishing a record linkage system between the risk factor records and death certificates.

The 16-year follow-up results of this census-population-based cohort study were used as the materials for the study.

RESULTS

In a large-scale cohort study carried out in Japan from 1966 to 1981, nonsmoking wives with smoking husbands were found to carry a significantly ele-

[1] Presented at the Symposium "Medical Perspectives on Passive Smoking," April 9–12, 1984, Vienna, Austria.

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vated risk of lung cancer (n = 200), nasal sinus cancer (n = 28), brain tumors (n = 34), and cancer of all sites (n = 2705).

Lung Cancer

A total of 429 deaths from lung cancer in women was recorded during the 16 years of follow-up (1966–1981). Of these deaths, 303 occurred among nonsmokers and 200 among 91,340 nonsmoking married women whose husbands' smoking habits were known.

The standardized mortality ratios (SMRs) of lung cancer in nonsmoking women were 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were nonsmokers, ex-smokers, or daily smokers of 1–14, 15–19, or 20 or more cigarettes per day, respectively (one-tail P value = 0.00178) (Table 1). A similar dose–response relationship was observed by age and occupation of the husband (Table 2).

This tendency is in sharp contrast with that of stomach cancer, where no relationship at all exists between the risk in nonsmoking wives and the amount of smoking by the husband (Tables 3 and 4, Figs. 1 and 2).

Similar trends of lung cancer risk elevation in nonsmoking women with the increase in the extent of the husband's smoking were observed in each time period of observation, in each age group, both by age of husbands and by age of wives, in each occupational group, and in most areas under observation (internal consistency) (Fig. 3) (7). No other characteristics of husbands or wives themselves were found to elevate the risk of lung cancer in their nonsmoking partners (7) (Table 5).

Nonsmoking husbands with smoking wives also showed an elevated risk of lung cancer, the SMRs being 1.00, 2.14, and 2.31 in nonsmoking wives, wives smoking 1–19 cigarettes, and wives smoking 20 or more cigarettes daily, respectively (P = 0.0177). This observation also strengthens the evidence listed above (Table 6).

TABLE 1

LUNG CANCER MORTALITY IN WOMEN BY AGE GROUP AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)[a]

Husband's age group	Husband's smoking habit										Total	
	Nonsmoker		Exsmoker		1–14/day		15–19/day		20+/day			
40–49	4	6.229	1	1.255	8	8.621	6	5.158	16	10.764	35	32.027
50–59	10	7.791	3	1.922	20	9.668	8	4.052	24	9.820	65	33.253
60–69	18	7.120	11	2.687	28	7.243	9	2.513	23	4.651	89	24.214
70–79	5	755	2	348	2	612	1	105	1	226	11	2.046
Total	37	21.895	17	6.212	58	26.144	24	11.828	64	25.461	200	91.540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		$1.36 < {}^{2.18}_{0.85}$		$1.42 < {}^{2.01}_{1.01}$		$1.58 < {}^{2.38}_{0.98}$		$1.91 < {}^{2.71}_{1.34}$		Mantel extension chi	2.915
					$1.45 < {}^{2.02}_{1.04}$						One-tail P value	0.00178
Mantel–Haenszel chi	—		1.0855		1.8290		3.0295					
One-tail P value			0.1389		0.0337		0.0012					

[a] Prospective study, 1966–1981, Japan.

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TABLE 2
LUNG CANCER MORTALITY IN WOMEN BY AGE GROUP, BY OCCUPATION, AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)*

Husband's occupation	Husband's age group	Husband's smoking habit: Nonsmoker		Exsmoker 1–19/day		Exsmoker 20+/day		Total	
Agricultural worker	40–49	1	2.502	6	5.941	9	3.636	16	12.079
	50–59	4	3.497	16	6.812	9	3.514	29	13.823
	60–69	13	4.084	33	6.845	10	2.152	56	13.081
	70–	3	323	1	446	0	89	4	858
Total		21	10.406	56	20.044	28	9.391	105	39.841
Other	40–49	3	3.727	9	9.093	7	7.128	19	19.948
	50–59	6	4.294	15	8.830	15	6.306	36	19.430
	60–69	5	3.036	15	5.598	13	2.499	33	11.133
	70–	2	432	4	619	1	137	7	1.188
Total		16	11.489	43	24.140	36	16.070	95	51.699
The weighted point estimate of rate ratio and test-based 90% confidence limits		1.00		1.41 < 1.94 / 1.03		1.93 < 2.74 / 1.35		Mantel extension chi	3.145
								One-tail P value	0.00083
Mantel–Haenszel chi		—		1.786		3.053			
One-tail P value				0.03705		0.00111			

* Prospective study, 1966–1981, Japan.

TABLE 3
STOMACH CANCER MORTALITY IN WOMEN BY AGE GROUP AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)*

Husband's age group	Husband's smoking habit: Nonsmoker		Exsmoker		1–14/day		15–19/day		20+/day		Total	
40–49	31	6.229	12	1.255	44	8.621	23	5.158	48	10.764	158	32.027
50–59	60	7.791	14	1.922	82	9.668	36	4.052	77	9.820	269	33.253
60–69	121	7.120	50	2.687	109	7.243	40	2.513	78	4.651	398	24.214
70–79	7	755	4	348	11	612	1	105	6	226	29	2.046
Total	219	21.895	80	6.212	246	26.144	100	11.828	209	25.461	854	91.540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.15 < 1.43 / 0.93		1.00 < 1.17 / 0.86		1.00 < 1.22 / 0.81		1.01 < 1.19 / 0.86		Mantel extension chi	−0.270
											One-tail P value	0.39358
Mantel–Haenszel chi	—		1.059		−0.016		−0.033		0.091			
One-tail P value			0.14480		0.49362		0.48684		0.46375			

* Prospective study, 1966–1981, Japan.

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TABLE 4
STOMACH CANCER MORTALITY IN WOMEN BY AGE GROUP, BY OCCUPATION, AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)*

Husband's occupation	Husband's age group	Husband's smoking habit: Nonsmoker		Exsmoker 1–19/day		20–/day		Total	
Agricultural worker	40–49	13	2.502	41	5.941	25	3.636	79	12.079
	50–59	37	3.497	56	6.812	37	3.514	130	13.823
	60–69	77	4.084	116	6.845	43	2.152	236	13.081
	70–	3	323	13	446	3	89	19	858
Total		130	10.406	226	20.044	108	9.341	464	39.841
Other	40–49	18	3.727	38	9.093	23	7.128	79	19.948
	50–59	23	4.294	76	8.830	40	6.306	139	19.430
	60–69	44	3.036	83	5.598	35	2.499	162	11.133
	70–	4	432	3	619	3	137	10	1.188
Total		89	11.489	200	24.140	101	16.070	390	51.699
The weighted point estimate of rate ratio and test-based 90% confidence limits		1.00		1.03 < 1.18 / 0.89		1.05 < 1.24 / 0.89		Mantel extension chi 0.234; One-tail P value 0.40749	
Mantel–Haenszel chi		—		0.298		0.486			
One-tail *P* value				0.38285		0.31348			

* Prospective study, 1966–1981, Japan.

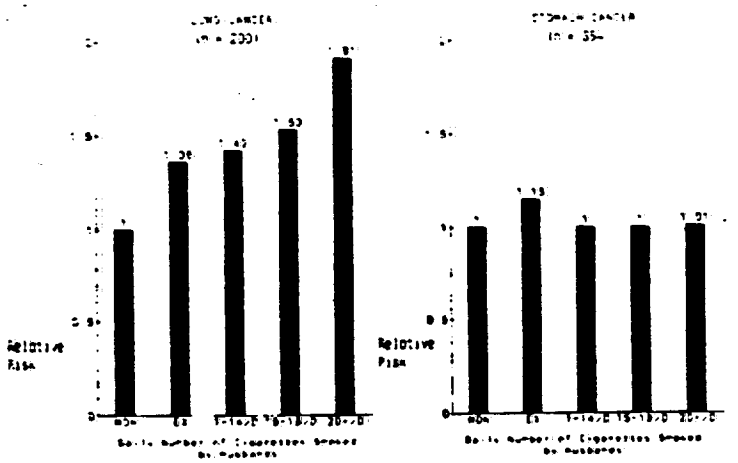

FIG. 1. Relative risks of lung cancer and stomach cancer in 91,540 nonsmoking wives by husbands' smoking habit. (Prospective Study, 1966–1981, Japan.)

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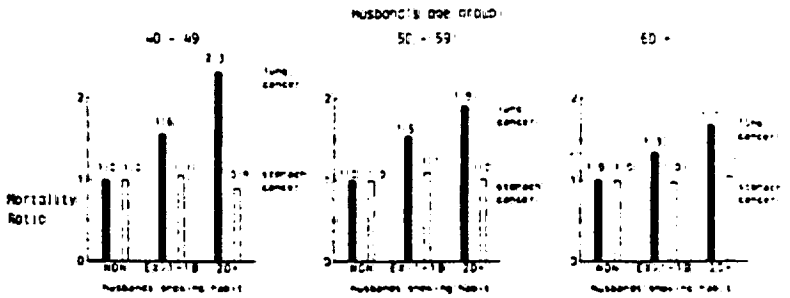

FIG. 2. Mortality ratios for lung cancer and stomach cancer in nonsmoking wives by husbands' smoking habits. (Prospective Study, 1966–1981, Japan.)

Nasal Sinus Cancer

A significant risk elevation of cancer of para nasal sinuses in nonsmoking wives was observed according to the amount that husbands smoked, the SMRs being 1.00, 1.67, 2.02, and 2.55 when husbands were nonsmokers or smokers of 10–14, 15–19, or 20 or more cigarettes daily, respectively ($P = 0.02482$) (Table 7). No other risk factors studied were identified as significantly altering the risk of nasal sinus cancer in women.

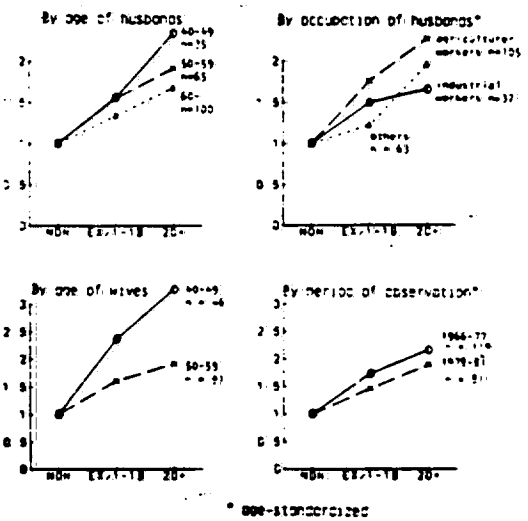

FIG. 3. Mortality ratios for lung cancer in nonsmoking wives by husbands' smoking habits. (Prospective Study, 1966–1981, Japan.)

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TABLE 5
LUNG CANCER MORTALITY IN NONSMOKING WOMEN: RATIO BY SELECTED RISK FACTORS[a]

	Mortality ratio (relative risk)	Chi-square values
Husband's characteristics		
Smoking (20 cig. +/day)	1.91	9.18
Drinking	1.06	0.04
Population density: 600-/-600	1.10	0.30
Women's characteristics		
Occupation: Agriculture/others	0.95	0.17
Number of children: 0-3/4-9	1.09	0.48
Drinking: +/-	1.02	0.01
Meat: Daily/others	1.12	0.09
Green-yellow vegetable: Daily/others	0.88	0.93
Soybean paste soup: Daily/others	1.08	0.29

[a] Prospective study, 1966-1981, Japan.

Brain Tumors

The risk of brain tumor was also observed to increase with an increase in the extent of husbands' smoking habits, the risk for nonsmoking women being 1.00, 3.03, 6.25, and 4.32 when husbands were nonsmokers or smokers of 1-14, 15-19, or 20 or more cigarettes daily, respectively ($P = 0.00376$) (Table 8).

Cancer of All Sites

In the case of cancers of all sites, a significant elevation in risk was observed, the SMRs for nonsmoking women being 1.00, 1.12, and 1.23 when husbands were nonsmokers, ex-smokers, or smokers of 1-19 or 20 or more cigarettes daily.

TABLE 6
LUNG CANCER MORTALITY IN NONSMOKING HUSBANDS BY WIVES' SMOKING HABIT[a]

Husband's age group	Wife's smoking habit: Nonsmoker		1-19/day		20+/day		Total	
40-59	24	10.741	1	321	1	184	26	11.246
60-	33	8.538	3	276	2	229	38	9.043
Total	57	19.279	4	597	3	413	64	20.289
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		$2.14 < {}^{4.65}_{0.98}$		$2.31 < {}^{5.94}_{0.90}$		Mantel extension chi	1.989
	1.00		$2.25 < {}^{4.22}_{1.19}$				One-tail P value	0.02335
Mantel-Haenszel chi			2.1046					
One-tail P value			0.0177					

[a] Prospective study, 1966-1981, Japan.

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TABLE 7
NASAL SINUS CANCER MORTALITY IN WOMEN BY AGE GROUP AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)*

Husband's age group	Husband's smoking habit: Nonsmoker		Ex-smoker		1–14/day		15–19/day		20+ day		Total	
40–49	0	6.229	0	1.255	1	8.621	1	5.158	2	10.764	4	32.027
50–59	1	7.791	0	1.922	3	9.668	1	4.052	2	9.820	7	33.253
60–69	4	7.120	0	2.687	5	7.243	2	2.513	6	4.651	17	24.214
70–79	0	755	0	348	0	612	0	105	0	226	0	2.046
Total	5	21.895	0	6.212	9	26.144	4	11.828	10	25.461	28	91.540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		—		1.67 < 4.20 / 0.67		2.02 < 6.33 / 0.64		2.55 < 6.27 / 1.04		Mantel extension chi: 1.963; One-tail P value: 0.02482	
Mantel–Haenszel chi	—		—		0.916		1.012		1.713			
One-tail P value					0.1783		0.15577		0.04336			

Note. In computation, ages 60–69 and 70–79 were combined.
* Prospective study, 1966–1981, Japan.

respectively ($P = 0.00020$) (Table 9). This risk elevation is influenced by the elevated risk of lung cancer and cancers of other selected sites such as nasal sinus cancer, brain tumor, and possibly also breast cancer. Risk elevation for cancer of all sites becomes nonsignificant when these cancers are excluded. No significant association was observed with other cancers such as those of the mouth, pharynx, esophagus, stomach, colon, rectum, liver, pancreas, peritoneum, cervix, ovary, urinary bladder, skin, bone, malignant lymphoma, or leu-

TABLE 8
BRAIN TUMOR MORTALITY IN WOMEN BY AGE GROUP AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)*

Husband's age group	Husband's smoking habit: Nonsmoker		Ex-smoker		1–14/day		15–19/day		20+ day		Total	
40–49	0	6.229	0	1.255	1	8.621	6	5.158	4	10.764	11	32.027
50–59	1	7.791	0	1.922	4	9.668	3	4.052	4	9.820	12	33.253
60–69	1	7.120	0	2.687	5	7.243	0	2.513	4	4.651	10	24.214
70–79	1	755	0	348	0	612	0	105	0	226	1	2.046
Total	3	21.895	0	6.212	10	26.144	9	11.828	12	25.461	34	91.540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		—		3.03 < 8.58 / 1.07		6.25 < 19.43 / 2.01		4.35 < 12.19 / 1.53		Mantel extension chi: 2.673; One-tail P value: 0.00376	
Mantel–Haenszel chi	—		—		1.756		2.656		2.317			
One-tail P value					0.03954		0.00395		0.01025			

Note. In computation, ages 60–69 and 70–79 were combined.
* Prospective study, 1966–1981, Japan.

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TABLE 9
ALL SITES CANCER MORTALITY IN WOMEN BY AGE GROUP, BY OCCUPATION, AND BY HUSBANDS' SMOKING HABIT (PATIENT HERSELF A NONSMOKER)*

Husband's occupation	Husband's age group	Husband's smoking habit: Nonsmoker		Exsmoker 1–19/day		20–/day		Total	
Agricultural worker	40–49	40	2.502	119	5.941	76	3.636	235	12.079
	50–59	96	3.497	201	6.812	115	3.514	412	13.823
	60–69	205	4.084	373	6.845	127	2.152	705	13.081
	70–	17	323	22	446	5	89	44	858
Total		358	10.406	715	20.044	323	9.391	1.396	39.841
Other	40–49	48	3.727	118	9.093	103	7.128	269	19.948
	50–59	79	4.294	248	8.830	169	6.306	496	19.430
	60–69	132	3.036	239	5.598	129	2.499	500	11.133
	70–	17	432	21	619	6	137	44	1.188
Total		276	11.489	626	24.140	407	16.070	1.309	51.699
The weighted point estimate of rate ratio and test-based 90% confidence limits		1.00		1.12 < 1.21 / 1.03		1.23 < 1.35 / 1.12		Mantel extension chi	3.540
								One-tail *P* value	0.00020
Mantel–Haenszel chi		—		2.232		3.628			
One-tail *P* value				0.01281		0.00014			

* Prospective study, 1966–1981, Japan.

kemia, the direction of this trend being evenly distributed to both the plus-side (risk increases with the extent of husband's smoking habit) and the minus-side (risk decreases with the extent of husband's smoking habit).

DISCUSSION

This study confirms the correlation between lung cancer and spousal smoking reported previously. The correlation is quite specific in terms of diseases. For instance, no risk elevation at all was observed for stomach cancer. A striking internal consistency of association was also observed. The results were essentially similar when observed in terms of age of husbands, age of wives, occupation of husbands, and differing periods of observation. The results are in line with a Greek study by Trichopoulos and others (10) and a U.S. study by Correa and others (4) (external consistency), although they are slightly at variance with an American Cancer Society study in the United States (5) and a case–control study conducted by Kabat and Wynder (8).

Differences in proximity between husband and wife in daily life, room size, room ventilation, and frequency of wives who work in offices in these countries are potentially influential factors in enhancing the extent of risk posed by husbands' smoking.

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Histology of 21 cases of lung cancer in nonsmoking wives with smoking husbands was not essentially different from that of smoking women (adenocarcinoma, 57.1%; squamous cell carcinoma, 19.0%; and small-cell carcinoma, 4.8%).

The current results of elevated risk of nasal sinus cancer in addition to the risk of lung cancer must strengthen the plausibility of carcinogenic hazards of sidestream smoke inhalation through the nose, as they are in line with the results of measurements of various carcinogens in sidestream smoke showing them to be present in higher concentrations than in mainstream smoke (2, 3). These results are also compatible with known evidence showing a possible influence of passive smoking on health including elevation of carboxyhemoglobin and nicotine/cotinine levels in saliva, blood, and urine after exposure to passive smoking; elevation of hydroxyproline levels in urine (a marker of collagen destruction in lung tissue); the presence of mutagens in urine (1); small airway dysfunction in those exposed daily to passive smoking in the workplace (11); and risk elevation for pneumonia, bronchitis, and asthma in children with smoking parent(s).

When the effects of passive smoking due to husbands' smoking were compared with the effects of direct smoking in women, the results clearly indicated that the effect of passive smoking is less than one-fifth that of direct smoking, the SMRs being 1.55 and 3.81, respectively. In terms of attributable risk, however, the effect of passive smoking on lung cancer in women is nearly as important as that of direct smoking because the population of intrahousehold passive smokers at risk is four times greater (n = 69,645) than the population of active smokers (n = 17,366). Therefore, although the relative risk of indirect smoking is much smaller than that of direct smoking, the absolute excess deaths from lung cancer due to passive smoking may be quite important because of the large size of the exposed group—especially in countries such as Japan where the majority (nearly 70%) of adult men smoke, but only a minority (15% or less) of adult women smoke.

Passive smoking can be divided into (a) direct passive smoking (direct inhalation of sidestream smoke before being diluted by room air) and (b) indirect passive smoking (inhalation of room air polluted by sidestream smoke) according to the extent of proximity effect, just as droplet infection is separated from droplet nuclei infection in acute respiratory communicable diseases: the effect of ventilation is of limited importance in the former case, although quite significant in the latter. Small room size and congested living conditions in Japan (and possibly also in countries like Greece) are naturally more conducive to direct passive smoking.

As described in a previous report, the age-adjusted mortality rates for lung cancer are increasing rapidly for both men and women in Japan. As only a fraction of Japanese women with lung cancer smoke cigarettes, the reasons why their mortality from lung cancer nearly parallels that of men have been unclear. The current study attempts to explain at least a part of this long-standing riddle. Although the average rate of female smokers in Japan has remained fairly stable over the past 20 years, a statistically significant increase in the mortality rate for lung cancer in nonsmoking women was observed in our long-term follow-up study of a large-size population. Mortality rates per 100,000 for ages 50–59, 60–69, and 70 and above were 7.1, 17.7, and 31.0 in first 10 years of follow-up and 9.9, 27.1,

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and 44.3 in the subsequent 6 years, respectively ($P = 0.00373$). This phenomenon can be interpreted as the influence of widespread exposure to passive smoking in Japan.

As also emphasized in this earlier report, these observations strongly question the validity of the conventional method of assessing the relative risk of developing lung cancer in smokers by comparing it with nonsmokers. This study shows that nonsmokers are definitely not a homogenous group and should be subdivided according to the extent of previous exposure to indirect or passive smoking. The observation of the effect of passive and active smoking on lung cancer risk in men and women revealed a similar effect of both active and passive smoking on lung cancer when nonsmokers without exposure to intrahousehold passive smoking were used as the unit risk group (Fig. 4).

The observation of an elevated risk of brain tumors in nonsmoking women with smoking husbands is of importance in considering the etiology of brain tumors (an area in which our current knowledge is quite limited), especially in relation to a similar report on the influence of passive smoking on childhood brain tumors (9).

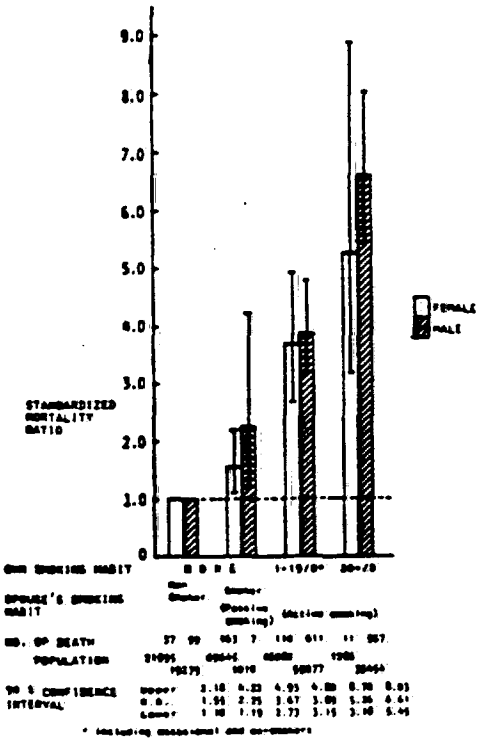

FIG. 4. Active and passive smoking and lung cancer mortality: Relative risks (RR) with 90% confidence intervals. (Prospective Study, 1966–1981, Japan.)

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The results of the present study must be effectively utilized in planning programs for the control of lung cancer and other selected diseases. The results clearly indicate that lung cancer, especially in women, can only be controlled satisfactorily when proper measures are taken against passive smoking as well as against active smoking, especially in countries like Japan. A similar statement may also be valid for cancers of other selected sites.

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Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking," Lung Cancer: Causes and Prevention, eds. M. Mizell and P. Correa (New York: Verlag Chimie International, 1984): 175-195.

This paper provides more of Hirayama's conclusions drawn from his large cohort study.

An overall RR of 1.45 (90% CI 1.04-2.02) was presented for nonsmoking women whose husbands smoked. A dose-response relationship with increasing number of cigarettes smoked by the husband was also claimed.

Hirayama reported a decreased risk for lung cancer in those women who consumed more green and yellow vegetables.

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Lung Cancer:

Causes and Prevention

Proceedings of the International Lung Cancer Update Conference, held in New Orleans, Louisiana, March 3-5, 1983

Edited by

Merle Mizell and **Pelayo Correa**

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CHAPTER 14

Lung Cancer In Japan: Effects of Nutrition and Passive Smoking

TAKESHI HIRAYAMA

Epidemiology Division, National Cancer Center, Research Institute, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan

ABSTRACT

Lung cancer is on a sharp increase in both men and women in Japan. Nonsmoking wives with smoking husbands were found to carry an elevated risk of lung cancer and ischemic heart disease by a large-scale cohort study, 1966-1981, for 265,118 adults in 29 Health Center Districts in Japan, the risk steadily going up with the increase in number of cigarettes smoked by the husband. In major cancers other than lung, no such risk elevation was observed. A nonsmoking husband with a smoking wife also showed an elevated risk of lung cancer. The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking just as for active smoking. Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking. Such risk reduction was not observed for ischemic heart disease. The observed results suggest that the influence of husband's smoking on nonsmoking wives in raising the risk of lung cancer is as a cancer promoter rather than a cancer initiator. This promoter hypothesis may explain why such continuous but low-dose exposure of passive smoking, which starts after adult age is reached, significantly elevates lung cancer risk in nonsmoking wives.

Key Words: Japan, cohort study, passive smoking, lung cancer, ischemic heart disease, green-yellow vegetables, β-carotene, promoter, promoter-inhibitor

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Lung Cancer Causes and Prevention

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Introduction

The mortality from lung cancer has been increasing rapidly in Japan (Figure 1). The number of deaths among males was 520 in 1947 and 17,555 in 1982, the corresponding number for females was 248 and 6661.

There exists little sign of a slowing down of the rate of increase, and the number of deaths from lung cancer are expected to exceed the number of deaths from stomach cancer in the near future. In parallel to this trend the number of cigarettes sold in Japan also has been on a sharp rise (Figure 1). The random sample survey conducted by the Tobacco Monopoly Corporation in 1982 revealed that currently 70.1% of adult males and 15.4% of adult females smoke in Japan.

The purpose of this chapter is to study the causative factors of lung cancer in Japan with special reference to the effect of passive smoking relative to the effect of active smoking. The possible influence of nutrition, β-carotene-rich green-yellow vegetables in particular, on the risk enhancing effect of active and passive smoking also is studied.

Methods

The materials of our ongoing large-scale cohort study for 265,118 adults aged 40 years and above in Japan were analyzed in detail to discover factors altering the

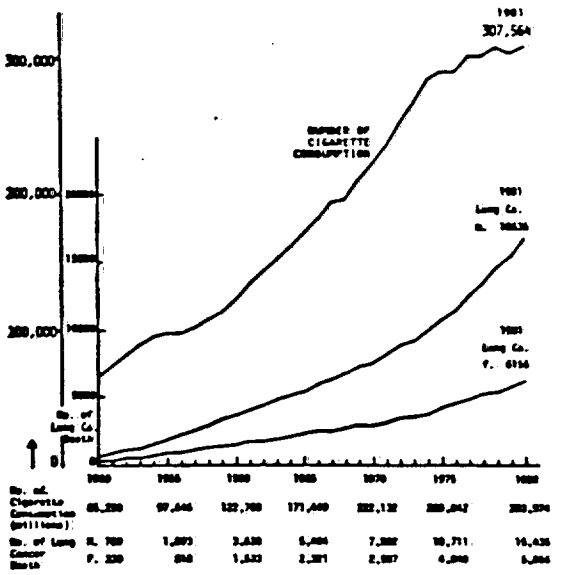

Figure 1. Trends in cigarette consumption and lung cancer deaths in Japan (1950–1981).

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risk of lung cancer in both men and women. For statistical analysis, programs included in the book *Epidemiologic Analysis with a Programmable Calculator* (U.S. Department of Health, Education and Welfare, 1979) mainly were used.

Results

Active Smoking and Lung Cancer Risk

Cigarette smoking was identified by far the most important cause of lung cancer in Japan, both by case-control studies conducted by the author and other researchers and by a large-scale cohort study (1–6) being conducted by the author for 265,118 adults (122,261 men and 142,857 women) aged 40 and above (95% of census population) in 29 Health Center Districts in Japan. These subjects were surveyed in October–December 1965 and followed up from January 1966 until December 1981. A clear-cut dose-response relationship was observed between the number of cigarettes ever smoked and the age-standardized mortality rate of lung cancer. The mortality rate of lung cancer also was found to be higher the earlier smoking was begun when age and total number of cigarettes ever smoked were standardized (Figure 2). The lung cancer-standardized mortality rate was observed

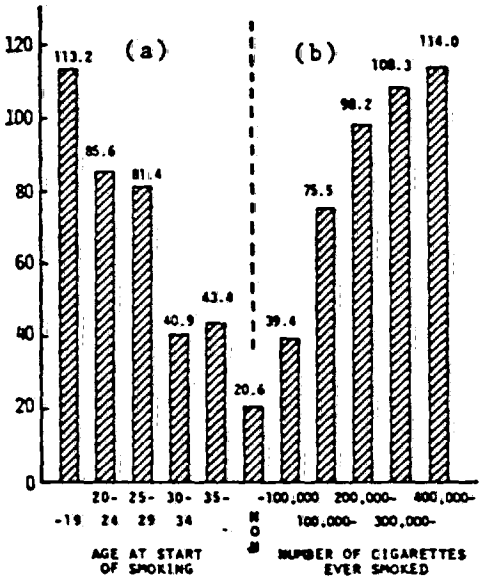

Figure 2. Lung Cancer. (a) Attained age- and amount of smoking-standardized mortality rate by age at start of smoking. (b) Attained age- and age at start of smoking-standardized mortality rate by total amount of cigarettes ever smoked. (Prospective study, 1966–1978 Japan.)

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to be 18.3% lower in smokers who do not inhale compared to regular deep inhalers, and 48.9% lower in smokers of filtertip cigarettes compared to smokers of nonfiltertip cigarettes, according to our cohort study. The risk of lung cancer in daily smokers also was noted to approach gradually that of nonsmokers with the lapse of years after smoking cessation, risk difference diminishing by 41.6% in 5 years after stopping the habit. This strongly suggests the major part of the influence of smoking during adulthood is the promoter action of substances included in mainstream smoke.

Effect of Nutrition on Active Smokers

Daily intake of green-yellow vegetables, rich in β-carotene, was found significantly to lower the risk of lung cancer (7, 8), particularly when the total amount of cigarettes ever smoked was less than 300,000 (6) (Figure 3). No other dietary habit showed such risk reduction. Risk reduction after smoking cessation appeared to be more pronounced in case of daily consumers of green-yellow vegetables. Taking similar evidence in laboratory studies into consideration, a promoter-inhibitor interaction model was conceptualized.

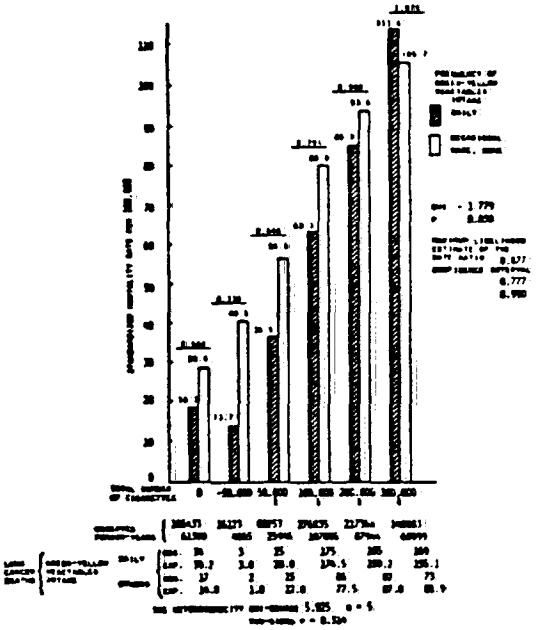

Figure 3. Standardized mortality rate for lung cancer by total number of cigarettes ever smoked and by frequency of green-yellow vegetable intake; males. (Prospective study, 1966–1978.)

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Passive Smoking and Lung Cancer

In the present cohort study (1966–1981), 427 deaths from lung cancer in women were recorded during 16 years of followup (1966–1981). Of these women, 269 were married, and 200 of these also were nonsmokers. These cases occurred among 91,540 nonsmoking married women whose husbands' smoking habits were studied. The risk of lung cancer was carefully measured, taking into consideration possible confounding variables. There was a statistically significant increased risk in relation to the extent of the husband's smoking (Figure 4), which confirmed the validity of previous reports (9, 10). The association was significant when observed by age of husbands (Table 1, Figures 1 and 5) and also by age of wives (Table 2). The further detailed analysis on materials cross-tabulated by age and occupation of the husband also confirmed the association (Table 3). The husband's drinking habits were noted to have no effect in raising the risk of lung cancer in nonsmoking wives (Table 4).

Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking also was observed with ischemic heart disease when observed by husband's age and occupation (Tables 5 and 6). The significant risk elevation of cancer of the nasal sinus also was observed in nonsmoking wives with husband's smoking. The risk elevation of emphysema and chronic bronchitis with spouse's smoking also was noted with borderline significance. However there was no tendency of risk elevation at all in major cancers other than lung (total of cancers of stomach, cervix, and breast), the standardized mortality rate in nonsmoking wives being almost exactly the same regardless of the husband's smoking habit (Table 7, Figure 6).

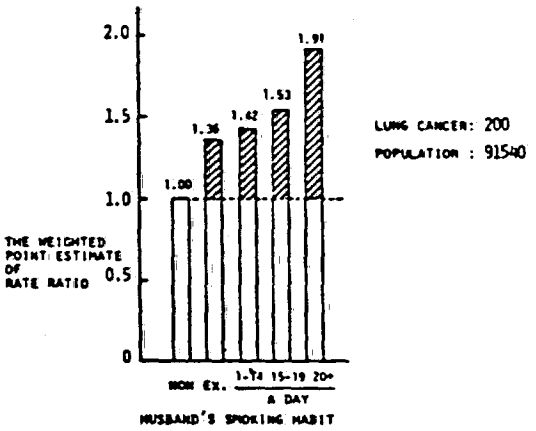

Figure 4. Age-standardized mortality rate ratio for lung cancer in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

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Table 1. Mortality rate for lung cancer in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966–1981, Japan[a]

Husband's age group	Husband's smoking habit: Nonsmoker No.	Nonsmoker Pop.	Ex-smoker No.	Ex-smoker Pop.	Number of cigarettes a day: 1-14/d No.	1-14/d Pop.	15-19/d No.	15-19/d Pop.	20+/d No.	20+/d Pop.	Total No.	Total Pop.
40–49	4	6,229	1	1,255	8	8,621	6	5,158	16	10,764	35	32,027
50–59	10	7,791	3	1,922	20	9,668	8	4,052	24	9,820	65	33,253
60–69	18	7,120	11	2,687	28	7,243	9	2,513	23	4,651	89	24,214
70–79	5	755	2	348	2	612	1	105	1	226	11	2,046
Total	37	21,895	17	6,212	58	26,144	24	11,828	64	25,461	200	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00	—	1.36	0.85 2.18	1.62	1.01 2.01	1.58	0.98 2.38	1.91	1.34 2.71	Mantel extension χ^2 2.915 one-tail p value 0.00178	
Mantel-Haenszel χ^2	—		1.0855		1.8290		3.0295					
one-tail p value			0.1389		0.0337		0.0012					

Table 2. Mortality rate for lung cancer in nonsmoking wives by smoking habit of husbands and by age group of wife: prospective study; 1966-1981, Japan[a]

Wife's age group	Husband's smoking habit: Nonsmoker No.	Nonsmoker Pop.	Ex-smoker: Number of cigarettes a day 1-19/d No.	1-19/d Pop.	20+/d No.	20+/d Pop.	Total No.	Total Pop.
40–49	4	7,918	21	17,492	21	12,615	46	38,025
50–59	14	7,635	46	15,640	31	8,814	91	32,089
60–69	16	6,170	31	10,381	10	3,793	57	20,344
70–79	3	172	1	671	2	239	6	1,082
Total	37	21,895	99	44,184	64	25,461	200	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00	—	1.43	0.99 2.01	1.74	1.19 2.55	Mantel extension χ^2 2.424 one-tail p value 0.00768	
Mantel-Haenszel χ^2	—		1.6042		2.3731			
one-tail p value			0.0543		0.0088			

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Table 3. Mortality rate for lung cancer in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)[a]

Husbands age (year)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥ 20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	4	6,229	15	15,034	16	10,764
	1		324		653	1	566
	2		90		231		293
	3	1	908	2	2,247	3	1,867
	4	1	476	1	993		1,044
	5	1	2,502	6	5,941	9	3,636
	6		46		165		108
	7		177	1	486	1	426
	8		1,112	3	3,431	2	2,241
	9		162	1	345		243
	10	1	432	1	542		340
50–59	Total	10	7,791	31	15,642	24	9,820
	1	1	345		593	2	446
	2		175		253	1	319
	3	1	817	5	1,764	1	1,324
	4	1	653	2	1,133	5	1,092
	5	4	3,497	16	6,812	9	3,514
	6		35		89		50
	7		120		273	1	234
	8	3	1,375	6	3,478	2	2,155
	9		164		378	1	251
	10		610	2	869	2	435
60–69	Total	18	7,120	48	12,443	23	4,651
	1		227	1	327	1	179
	2	1	91		143		124
	3		305	2	594	2	327
	4	2	508	5	822	1	500
	5	13	4,084	33	6,845	10	2,152
	6		9		31		14
	7		45		82		55
	8	1	805	5	1,784	4	736
	9		121	1	208		92
	10	1	925	1	1,607	5	472
70 +	Total	5	755	5	1,065	1	226
	1		32		30		5
	2		21		14		4
	3		18	1	36		8
	4		48		73		20
	5	3	323	1	446		89
	6		1		1		0
	7		1		5		1
	8		87	2	119	1	36
	9		11		19		2
	10	2	213	1	322		61
[a] Standardized Risk Ratio		1.000		1.436		1.872	

Mantel extension χ^2: 3.124; one-tail p value: 0.00089.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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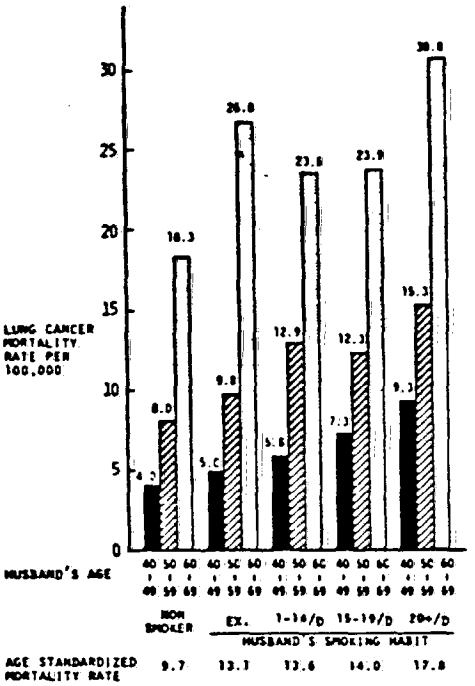

Figure 5. Age-specific mortality rate for lung cancer per 100,000 in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

Table 4. Mortality rate for lung cancer in women by age group and by alcohol drinking habits of husband: (patient herself a nonsmoker): prospective study, 1966–1981, Japan

Husband's age group	Husband's drinking habits: Nondrinker No.	Nondrinker Pop.	Occas. Rare No.	Occas. Rare Pop.	Daily No.	Daily Pop.	Obscure No.	Obscure Pop.	Total No.	Total Pop.
40–49	12	6,141	10	15,877	13	9,935	0	74	35	32,027
50–59	12	7,437	29	14,666	24	10,786	0	364	65	33,253
60–69	23	6,741	35	9,234	27	7,606	4	633	89	24,214
70–79	1	686	5	666	4	589	1	105	11	2,046
Total	48	21,005	79	40,443	68	28,916	5	1,176	200	91,540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00	—	1.03	1.61 / 0.66	1.11	1.59 / 0.77				
Mantel-Haenszel χ^2 one-tail p value	—		−0.1019	0.4594	0.4564	0.3240			Mantel extension χ^2 0.626 one-tail p value 0.26566	

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 5. Mortality rate for ischemic heart diseases in women by age group and by smoking habits of husband: prospective study, 1966–1981, Japan

Husband's age group	Husband's smoking habit: Nonsmoker No.	Nonsmoker Pop.	Ex-smoker 1-19/d No.	Ex-smoker 1-19/d Pop.	20+/d No.	20+/d Pop.	Total No.	Total Pop.
40–49	13	6,229	40	15,034	33	10,764	86	32,027
50–59	26	7,791	56	15,642	49	9,820	131	33,253
60–69	65	7,120	125	12,443	47	4,651	237	24,214
70–79	14	755	19	1,065	7	226	40	2,046
Total	118	21,895	240	44,184	136	25,461	494	91,540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.10	1.33 0.91	1.31	1.63 1.06		
Mantel-Haenszel χ^2 one-tail p value	—		0.8504 0.1976		2.0723 0.0191		Mantel extension χ^2 2.073 one-tail p value 0.01909	

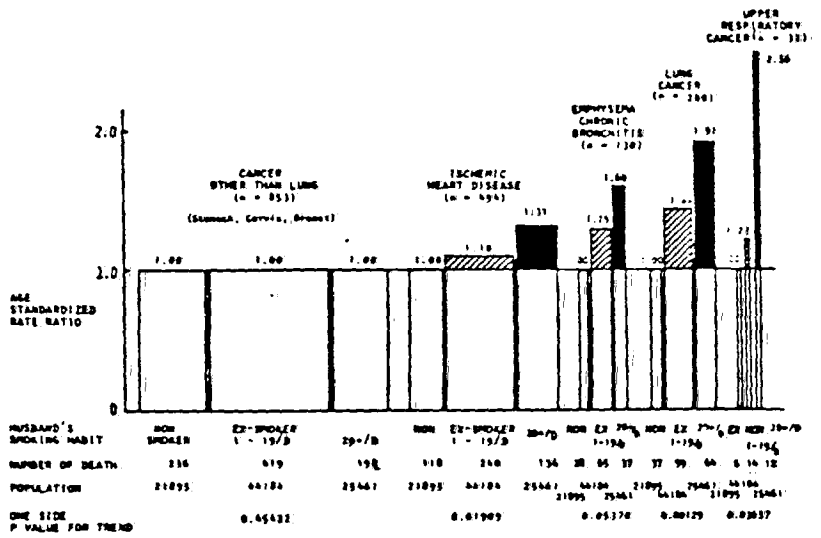

Figure 6. Standardized mortality rate ratio for selected causes of death in 91,540 nonsmoking women by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

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Table 6. Mortality rate for ischemic heart disease in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)[a]

Husbands age (years)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥ 20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	13	6,229	40	15,034	33	10,764
	1	1	324		653	1	566
	2		90	1	231		293
	3		908	4	2,247	1	1,867
	4		476	1	993	5	1,044
	5	8	2,502	25	5,941	18	3,636
	6		46		165		108
	7	1	177	2	486		426
	8		1,112	7	3,431	6	2,241
	9		162		345	1	243
	10	3	432		542	1	340
50–59	Total	26	7,791	56	15,642	49	9,820
	1	1	345	3	593		446
	2	2	175		253		319
	3	2	817	5	1,764	6	1,324
	4		653	6	1,133	4	1,092
	5	15	3,497	27	6,812	26	3,514
	6		35	1	89		50
	7		120	1	273	2	234
	8	5	1,375	8	3,478	11	2,155
	9		164	1	378		251
	10	1	610	4	869		435
60–69	Total	65	7,120	125	12,443	47	4,631
	1	2	277	2	327	1	179
	2	1	91	2	143	1	124
	3	2	305	5	594	1	327
	4	10	508	8	822	5	500
	5	36	4,084	79	6,845	27	2,152
	6		9	1	31		14
	7	1	45	1	82	1	55
	8	7	805	13	1,784	6	736
	9	1	121	2	208		92
	10	5	925	12	1,607	5	472
70+	Total	14	755	19	1,065	7	226
	1	2	32	1	30		5
	2	2	21		14	1	4
	3		18	1	36		8
	4	1	48	1	73		20
	5	5	323	11	446	2	89
	6		1		1		0
	7		1		5		1
	8		87	1	119	3	36
	9		11	2	19		2
	10	4	213	2	322	1	61
[a] Standardised Risk Ratios	—	1.000		1.103		1.359	

Mantel extension χ^2: 2.351; one-tail p value: 0.00936.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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Table 7a. Mortality rates for major cancers other than lung in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966–1981, Japan[a]

Husband's age group	Husband's smoking habit (cigarettes a day)							
	Nonsmoker		Ex-smoker 1–19		20+		Total	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40–49	44	6,229	117	15,034	71	10,764	232	32,027
50–59	97	7,791	191	15,642	119	9,820	407	33,253
60–69	160	7,120	274	12,443	106	4,651	540	24,214
70–79	14	755	20	1,065	8	226	42	2,046
Total	315	21,895	602	44,184	304	25,461	1,221	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.00	1.11 0.90	1.00	1.05 0.95		
Mantel-Haenszel χ^2	—		−0.0015		0.0449		Mantel extension χ^2 0.115	
one-tail p value			0.4994		0.4821		one-tail p value 0.4542	

Table 7 b. Mortality rates for major cancers other than lung in women by age, occupation, and smoking habit of the husband (patient herself a nonsmoker)[a]

Husbands age (years)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥ 20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	45	6,229	120	15,034	74	10,764
	1	2	324	1	653	3	566
	2		90	1	231	2	293
	3	9	908	17	2,247	12	1,867
	4	3	476	8	993	8	1,044
	5	17	2,502	59	5,941	35	3,636
	6		46		165		108
	7	1	177	6	486		426
	8	10	1,112	21	3,431	13	2,241
	9	1	162	4	345	1	243
	10	2	432	3	542		340
50–59	Total	98	7,791	195	15,642	122	9,820
	1	13	345	2	593	3	446
	2	2	175	1	253	1	319
	3	14	817	16	1,764	10	1,324
	4	1	653	18	1,133	9	1,092
	5	49	3,497	81	6,812	56	3,514
	6		35		89		50
	7	2	120	4	273	2	234
	8	12	1,375	49	3,478	31	2,155
	9		164	7	378	4	251
	10	5	610	17	869	6	435
60–69	Total	161	7,120	227	12,443	106	4,651
	1	5	227	5	327	2	179
	2	3	91	3	143	3	124
	3	7	305	11	594	5	327
	4	5	508	28	822	12	500
	5	102	4,084	158	6,845	58	2,152

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 7 b. (cont.)

Husbands age (years)	Occupation[b]	Nonsmoker No.	Nonsmoker Pop.	Ex-smoker or 1–19/day No.	Ex-smoker or 1–19/day Pop.	≥ 20/day No.	≥ 20/day Pop.
	6		9	1	31		14
	7	1	45	3	82	2	55
	8	10	805	40	1,784	17	736
	9	2	121	3	208		92
	10	24	925	25	1,607	7	472
70 +	Total	14	755	21	1,065	8	226
	1		32		30		5
	2	1	21		14		4
	3	1	18		36		8
	4		48	1	73	2	20
	5	7	323	15	446	4	89
	6		1		1		0
	7		1		5		1
	8	1	87	2	119	1	36
	9		11		19		2
	10	4	213	3	322	1	61
[a] Standardised Risk Ratios		1.000		0.969		1.034	

Mantel extension χ^2: −0.129; one-tail p value: 0.44868.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

Comparison of the Effects of Active Smoking and Passive Smoking

When the risk of lung cancer in nonsmokers with nonsmoking spouses was taken as a unit, a definite dose-response relationship was observed, the highest risk being in heavy active smokers, followed by mild active smokers, then heavy passive smokers, and then mild passive smokers (Figure 7). The risk gradient was similar both in men and in women (Figure 8). A significantly elevated risk of lung cancer also was noted for nonsmoking husbands with smoking wives.

Because the size of population exposed to passive smoking is quite large in the case of women, the effect of passive smoking because of the husband's smoking was estimated as 65% of that of active smoking. Our recent survey showed that 47.5% and 32.6% of Japanese adult women were being exposed to passive smoking at home and at the workplace, respectively (Figure 9). Therefore it must be a sound estimate that the total effect of passive smoking is approximately equivalent to that of active smoking in women. However, as a majority of adult men are still smokers, the total effect of passive smoking relative to active smoking must be on

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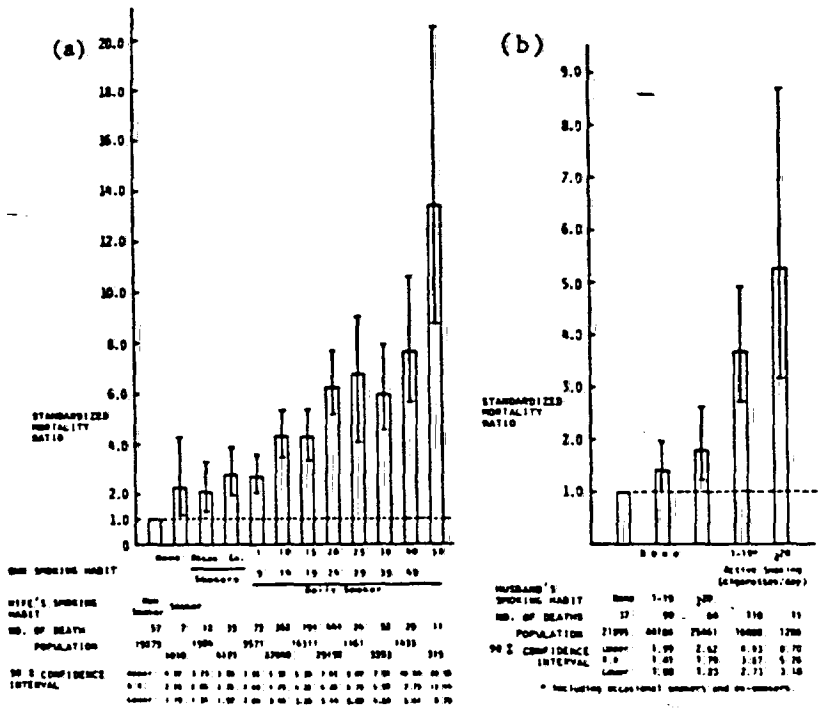

Figure 7. (a) Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals; males.(Prospective study, 1966–1981, Japan.) (b) Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals; females. (Prospective study, 1966–1981, Japan.)

the order of a few percent. The effect on lung cancer risk of passive smoking at home in relation to active smoking for men was calculated as 0.4% in our series.

Effect of Nutrition on Passive Smokers

A significantly lower risk of lung cancer was observed when nonsmoking wives with smoking husbands consumed green-yellow vegetables daily (Tables 8 and 9, Figures 10 and 11) suggesting that the promoter-inhibitor interaction model also applied to passive smoking just as in active smoking (Figure 9). Such risk reduction caused by daily intake of green-yellow vegetables was not observed for ischemic heart disease (Table 10, Figure 12).

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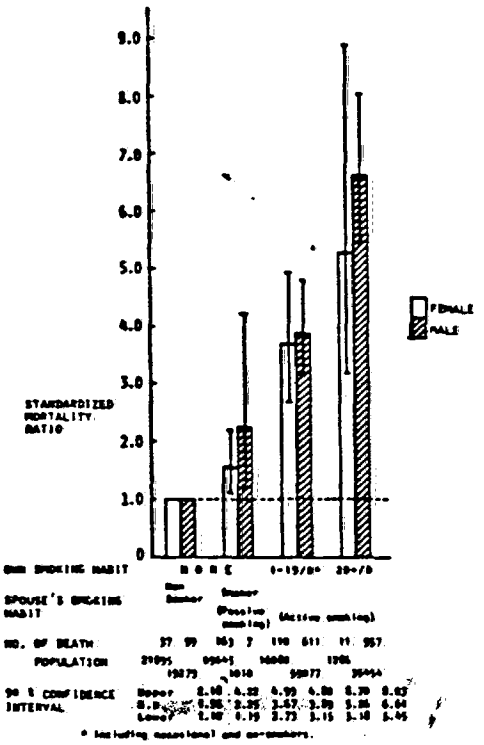

Figure 8. Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals. (Prospective study, 1966–1981, Japan.)

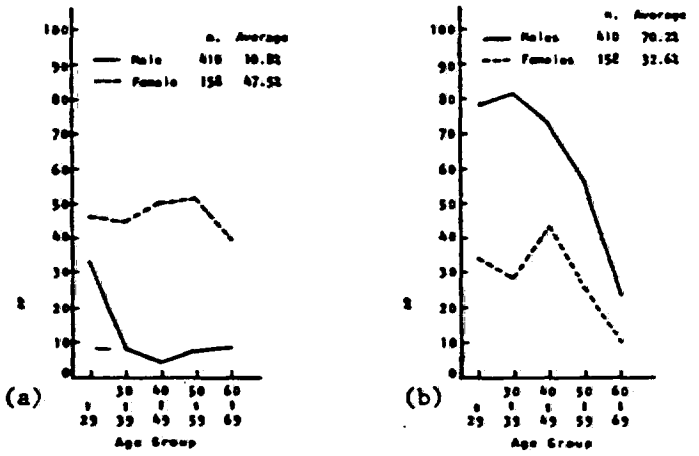

Figure 9. (a) Percentage of nonsmokers exposed to sidestream smoke at home, Japan, 1983. (b) Percentage of nonsmokers exposed to sidestream smoke at the workplace, Japan, 1983.

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Table 8. Lung cancer mortality rate in nonsmoking wives by smoking habit of the husband: comparison between daily and non daily intake of green-yellow vegetables

Husband's smoking habits		Nonsmoker				Ex-smoker on 1-19 day				≥ 20/day			
Wife's eating habits		Green-yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.
Occupation	Age												
Agriculture	40–49	1,958	1	544	0	5,050	5	891	1	3,037	7	599	2
	50–59	2,805	4	692	0	5,196	11	1,616	5	2,588	9	926	0
	60–69	3,359	7	725	6	5,106	22	1,739	11	1,588	6	564	4
	70–79	258	3	65	0	287	1	159	0	45	0	44	0
Others	40–49	2,422	3	1,305	0	7,288	8	1,805	1	5,377	5	1,751	2
	50–59	3,181	5	1,113	1	6,732	12	2,098	3	4,633	5	1,673	10
	60–69	2,266	4	770	1	4,088	9	1,510	6	1,906	10	593	3
	70–79	216	2	216	0	371	1	248	3	81	1	56	0
Total		16,465	29	5,430	8	34,118	69	10,066	30	19,255	43	6,206	21

Grand total	Population: 91540	Lung cancer: 200

Green-yellow vegetables	Mantel-extension χ^2	P-value (two tailed)
Daily	2.072	0.03827
Nondaily	2.487	0.01288
Total	3.090	0.00200

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 9. Effect of daily intake of green-yellow vegetables on lung cancer mortality in nonsmoking wives with smoking husbands[a]

Husband's smoking habit		Ex-smoker or 1–19/day				≥ 20/day			
Wife's eating habit		Green-yellow vegetables							
		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.
Occupation	Age								
Agriculture	40–49	5,050	5	891	1	3,037	7	559	2
	50–59	5,196	11	1,616	5	2,588	9	926	0
	60–69	5,106	22	1,739	11	1,588	6	564	4
	70–79	287	1	159	0	45	0	44	0
Others	40–49	7,288	8	1,805	1	5,377	5	1,751	2
	50–59	6,732	12	2,098	3	4,633	5	1,673	10
	60–69	4,088	9	1,510	6	1,906	10	593	3
	70–79	371	1	248	3	81	1	56	0
Total		34,118	69	10,066	30	19,255	43	6,206	21

[a]Mantel-Haenszel χ^2: = 1.986, p (two-tailed 0.047). Odds ratio: Nondaily green-yellow vegetable intaker, 1.000; daily green-yellow vegetables intake, 0.707 (standardized rate ratio); 90% confidence limits, 0.538–0.943.

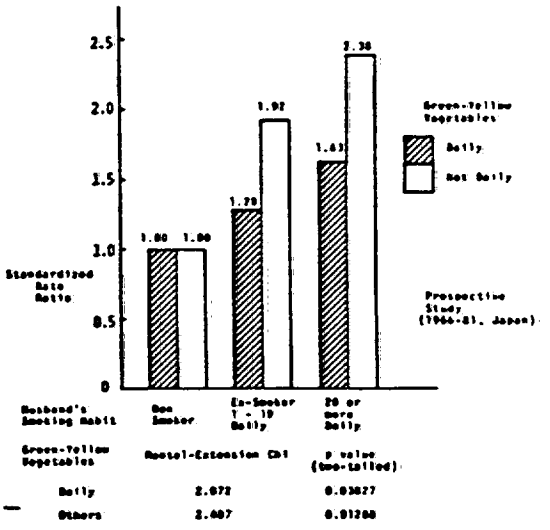

Figure 10. Lung cancer mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

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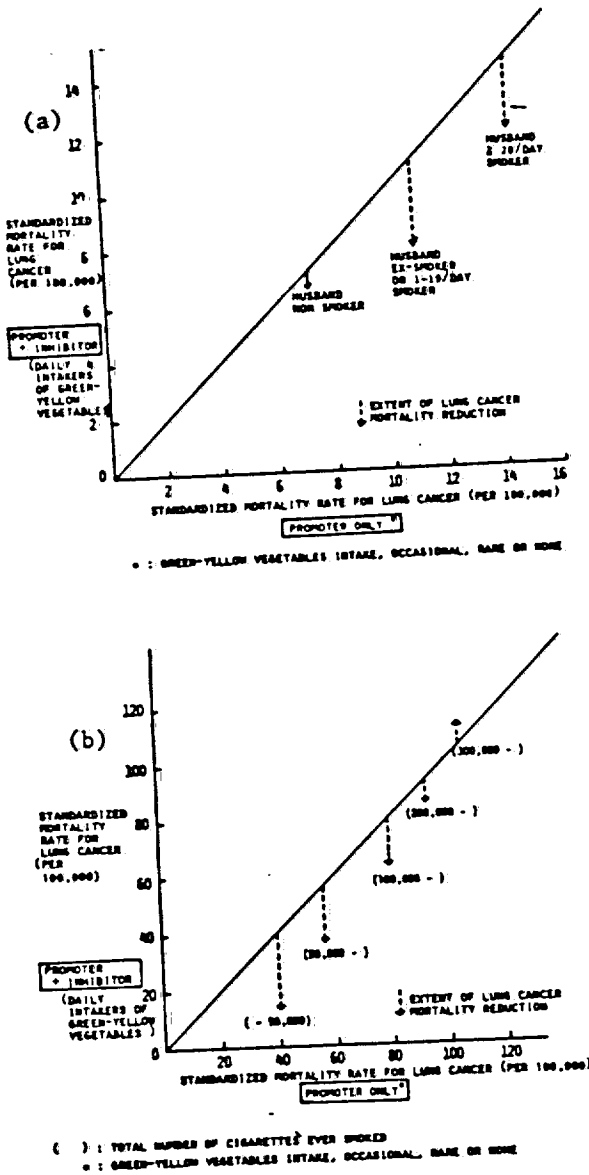

Figure 11. (a) Standardized mortality rate for lung cancer in nonsmoking wives by smoking habit of the husband. Comparison between daily and nondaily intake of green-yellow vegetables. (Prospective study, 1966–1981, Japan.) (b) Standardized mortality rate for lung cancer according to total number of cigarettes smoked and frequency of consumption of green-yellow vegetables; males. (Prospective study, 1966–1978, Japan.)

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Table 10. Ischemic heart disease mortality rate in nonsmoking wives by smoking habit of the husband: comparison between green-yellow vegetables intake daily and nondaily

Husband's smoking habit		Nonsmoker				Ex-smoker or 1–19/day				≥ 20/day			
Wife's eating habit		Green-yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.
Occupation	Age												
Agriculture	40–49	1,958	6	544	2	5,050	18	891	7	3,037	14	599	4
	50–59	2,805	11	692	4	5,196	25	1,616	2	2,588	21	926	5
	60–69	3,359	30	725	6	5,106	55	1,739	24	1,588	21	564	6
	70–79	258	2	65	3	287	10	159	1	45	2	44	0
Others	40–49	2,422	3	1,305	2	7,288	10	1,805	5	5,377	12	1,751	3
	50–59	3,181	8	1,113	3	6,732	18	2,098	11	4,633	17	1,673	6
	60–69	2,266	21	770	8	4,088	33	1,510	13	1,906	11	593	9
	70–79	216	7	216	2	371	6	248	2	81	3	56	2
Total		16,465	88	5,430	30	34,118	175	10,066	65	19,255	101	6,206	35
Grand total		Population: 91540				Ischemic heart disease: 494							

Green-yellow vegetables	Mantel-extension χ^2	P value (two tailed)
Daily	2.307	0.02105
Nondaily	0.820	0.41222
Total	2.406	0.01613

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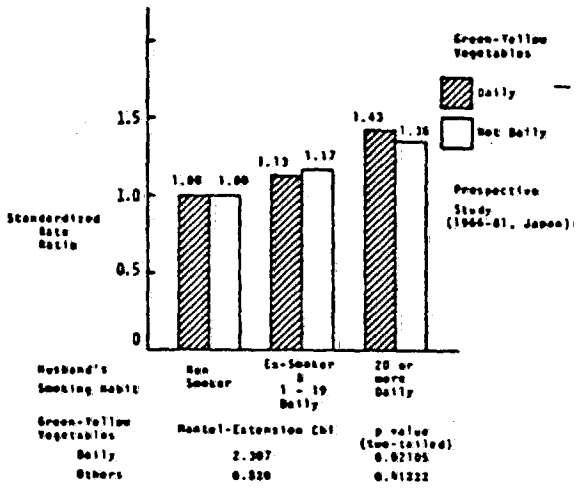

Figure 12. Ischemic heart disease mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

Discussion

The age-adjusted mortality rates for lung cancer have been sharply increasing both for men and for women in Japan. As only a fraction of Japanese women with lung cancer smoke cigarettes, the reasons for the trend of their mortality from lung cancer have been unclear. The present study appears to explain at least a part of this long-standing riddle.

This observation also questions the validity of the conventional method of assessing the relative risk of developing lung cancer in smokers by comparing them with nonsmokers. This study shows that nonsmokers are not a homogeneous group and should be subdivided according to the extent of previous exposure to indirect or passive smoking. Although the relative risk of indirect smoking was smaller than that of direct smoking, the absolute excess deaths from lung cancer resulting from passive smoking must be important because of the large size of the exposed group. Therefore, these results of our current study must be of public health importance, strengthening already existing evidence for a health hazard from passive smoking (11-13) (Table 11).

As shown in Figure 9, 47.5% and 32.6% of 158 nonsmoking adult women surveyed recently are noted to be exposed to sidestream smoke at home and at the workplace, respectively. One survey conducted in Aichi prefecture in Japan showed that nonsmoking wives are exposed to their husband's smoking 6.7 times a day on the average.

Because sidestream smoke contains varieties of cancer promoters at higher concentration than does mainstream smoke, it must be reasonable to consider the

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Table 11. Passive smoking is harzardous to health

1. Existence of toxic substances (including carcinogens) in sidestream smoke mostly at higher concentration than in mainstream smoke.
2. Existence of a large number of nonsmokers who have to inhale sidestream smoke frequently and intensively for long years at home and/or at the workplace.
3. Existence of sidestream smoke component in blood and urine of nonsmokers exposed to passive smoking, (eg, nicotine, CO-Hb in blood and Mutagens in urine.).
4. Existence of functional abnormalities in nonsmokers exposed heavily to passive smoking (eg, respiratory or circulatory function).
5. Lung tissue damage and destruction in chronic passive smokers as shown by elevated hydroxyproline excretion in urine.
6. Higher incidence of selected diseases in nonsmokers exposed heavily to passive smoking (eg, pneumonia, bronchitis, asthma, ischemic heart disease, lung and nasal sinus cancer).
7. Experimental evidence.

main effect of passive smoking on lung cancer risk results from the prolonged exposure to such promoters in sidestream smoke. The risk-inhibitory effect of a daily intake of green-yellow vegetables that are rich in β-carotene must be considered as an additional evidence for such a promoter action hypothesis of passive smoking. The hypothesis also explains why exposure to passive smoking that starts after reaching adult age can significantly influence the risk of lung cancer.

The histology of 21 cases of lung cancer in nonsmoking wives of smoking husbands was not essentially different from that in smoking women (adenocarcinoma 57.1%, squamous cell carcinoma 19.0%, and small-cell carcinoma 4.8%). A case-control study conducted within our cohort study revealed a significant dose-response relationship between adenocarcinoma of the lung and the number of cigarettes smoked daily, relative risk being 1.39 and 5.75 for smokers of 1-14 and 15 or more cigarettes daily, the chi square for the trend being 6.848 with a one-tail p value of 0.004. Therefore the predominance of adenocarcinoma of the lung in nonsmoking women with smoking husbands should not be considered unfavorable evidence for promoter action hypothesis of passive smoking. In passive smoking, sidestream smoke usually is inhaled through the nose, whereas in active smoking mainstream smoke always is inhaled through the mouth. This difference could be a reason for the elevated risk of nasal sinus cancer in passive smokers. The mechanism of the action of passive smoking on the risk of ischemic heart disease, however, must be explained in different ways (eg, a combined action of carbon monoxide and nicotine).

In summary, to reduce the effect of active and passive smoking and to encourage the effect of nutrition, in particular β-carotene intake, would be the most productive course for lung cancer prevention. For selected persons exposed to other known carcinogens, eg, those related to occupation or radiation, such environmental exposure also must be minimized in addition to the preventive measures focused on lifestyle variables given above.

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Trichopoulos, D., Kalandidi, A., Sparros, L. and MacMahon, B., "Lung Cancer and Passive Smoking," International Journal of Cancer 27(1): 1-4, 1981.

This case-control study included 51 women admitted to three large hospitals in Athens with a final diagnosis of lung cancer other than adenocarcinoma or terminal bronchial (alveolar) carcinoma. Of these, 14 were histologically confirmed and 19 cytologically confirmed. Controls (163 in all) came from a different hospital, one for orthopedic disorders. The study is described as reporting observations suggestive of lung cancer as an effect of "passive exposure" to cigarette smoke.

Only 23 cases were married to current smokers. RRs for spousal smoking habit were presented as 2.4, for husbands smoking 1-20 cigarettes per day and 3.4, for husbands smoking >20 cigarettes per day. No CIs are presented.

The authors acknowledge the small sample size and preliminary nature of this report.

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Int. J. Cancer: 27, 1-4 (1981)

LUNG CANCER AND PASSIVE SMOKING

Dimitrios TRICHOPOULOS[1], Anna KALANDIDI[1], Loukas SPARROS[1] and Brian MACMAHON[2,3]

[1] *Department of Hygiene and Epidemiology, University of Athens School of Medicine, Athens, Greece;* [2] *Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.*

Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were non-smokers. Among the non-smoking women there was a statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted.

Acute and chronic effects on lung function and the cardiovascular system have been noted in non-smokers involuntarily or passively exposed to the cigarette smoke of others (Aronow, 1978; Lenfant and Liu, 1980). We report observations suggesting that the effects of such exposure may include the most notorious health consequence of smoking among smokers themselves - carcinoma of the lung.

MATERIAL AND METHODS

This is a case-control study. The cases were all of the female, Caucasian patients, registered as residents of Athens, who were admitted to any of three large hospitals in Athens, between September 1978 and June 1980, with a final diagnosis of lung cancer other than adenocarcinoma or terminal bronchial (alveolar) carcinoma. The hospitals were the largest chest hospital of Athens ("Sotiria"), the largest cancer hospital ("Agios Savas") and the only other hospital exclusively for cancer patients ("Agii Anargyri"). Of the 51 cases identified, 14 were histologically and 19 cytologically confirmed, while in 18 the diagnosis was based on clinical and radiological evidence. Diagnosis of adenocarcinoma can confidently be excluded in the 14 histologically confirmed cases. It is possible that some adenocarcinomas are included among the 19 cytologically diagnosed cases and probable that there are some among the 18 clinically diagnosed patients. However, even in unselected clinical series of lung cancer cases among women in Greece, adenocarcinomas and alveolar carcinomas do not represent more than one-third of cases (Papacharalampous, personal communication): the number in our series is therefore not likely to be more than seven or eight.

Comparison patients (controls) were hospitalized during the same time period in the Athens Hospital for Orthopedic Disorders (KAT). This hospital is located in the same area of Athens as those which were the sources of the cases. The hospitals from which the cases came were considered unsuitable as sources of controls because of the high proportion of patients with other diseases of the lungs and other smoking-related diseases: we did not wish to have the interviewer judge, on a case-by-case basis, the suitability of a patient for control purposes. Six times during the time-period of the study, the same physician who interviewed the cases visited the Hospital for Orthopedic Disorders and interviewed all the available adult women patients in two departments of the hospital. Non-Caucasian patients and patients not registered as residents of Athens were not included. Of the 163 controls so ascertained, 108 were being treated for fractures, 18 for osteoarthrosis and 37 for other bone and joint diseases.

All cases and comparison patients (controls) were interviewed by the same physician. They were asked about the smoking habits of themselves and their husbands. Specifically, they were asked when they started smoking, if and when they stopped and what was the average number of cigarettes smoked daily; the same questions were asked about their husbands. Those who had stopped smoking 5-20 years before the interview were classified as ex-smokers; those who had stopped smoking within 5 years of the interview were considered as current smokers; and those who stopped smoking more than 20 years previously were classified as non-smokers. For the computation of the total number of cigarettes smoked by her husband, a woman's exposure was considered to start with her marriage and to end when she was divorced, or when the husband died or stopped smoking. A change of husband was considered as a change in the husband's smoking habits (if the two were in fact different), and singleness was considered the equivalent of marriage to a non-smoker.

Statistical significance is assessed by the X^2 for linear trend in proportions, as described by Armitage (1971).

RESULTS

Demographic characteristics of the cases and controls are compared in Table 1. The groups are similar in age, as indicated by the distributions in Table 1 and means of 61.7 for cases and 62.1 for controls. Duration of marriage, occupation, socioeconomic status (as measured by years of schooling) and recent residence are not notably or significantly different between cases and controls. It is, therefore, not necessary to stratify for these variables in the analysis particularly since none is significantly associated

[3] To whom reprint requests should be addressed.

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TABLE I

DEMOGRAPHIC CHARACTERISTICS OF THE CASE AND CONTROL PATIENTS

Characteristic	Number		Percentage	
	Cases	Controls	Cases	Controls
Total number	51	163	100.0	100.0
Age:				
<50 years	7	21	13.7	12.9
50–69 years	30	98	58.8	60.1
70+ years	14	44	27.5	27.0
Never married	1	15	2.0	9.2
Duration of marriage[1]:				
<20 years	8	33	16.0	22.3
20–39 years	31	70	62.0	47.3
40 years	11	45	22.0	30.4
Occupation:				
Housewife	32	96	62.7	58.9
Agriculture or labor	12	44	23.5	27.0
Schooling of 6+ years	19	71	37.3	43.6
Recent residence[2]:				
Urban	34	101	66.7	62.0
Semi-urban	3	13	5.9	8.0
Rural	14	49	27.5	30.1

[1] Percentages of the married. – [2] All patients were registered as resident in Athens, but some had changed residence recently, perhaps in connection with their need for medical care. Classified according to standard classification of the Greek National Statistical Service.

with smoking in these data. The duration of schooling of the husband was slightly longer in controls than in cases (65.0% 6 years or more, compared to 54.9%) but again was not related to smoking habit.

Among the 51 women with lung cancer, 11 were smokers, whereas among the 163 control women 14 were smokers, giving a relative risk associated with smoking of 2.9. These 25 women were excluded from the following analysis. The mean age of the remaining 40 lung cancer patients was 62.8 years and of the 149 remaining control women 62.3 years. Among non-smokers, control women were of only slightly higher socioeconomic status than the cancer patients - 63% of their husbands had finished primary school, compared to 58% among the controls.

Table II shows the distribution of non-smoking women with lung cancer and of non-smoking control women according to current smoking habits of their husbands. There is a statistically significant association between the husband's smoking and a woman's lung cancer risk. A non-smoking woman whose husband is a regular smoker has a risk of developing lung cancer which is twice as high as that of a non-smoking woman married to a non-smoker.

Table III shows the distribution of non-smoking women with lung cancer and of non-smoking control women according to the estimated total number of cigarettes smoked by their husbands by the time of the interview. It may be noted that there are only 64 women in the "zero" category since the husbands of three women with lung cancer and of 15 controls died, or divorced their wives, or stopped smoking, more than 20 years ago and thus were classified among the non-smokers in Table II. There is a statistically significant association between total number of cigarettes smoked by the husband and a woman's lung cancer risk. The association between husband's smoking habits and wife's lung cancer risk was examined separately for patients with or without cytological confirmation of the cancer. The slope of the linear trend was practically identical in the two groups.

TABLE II

SMOKING HABITS OF HUSBANDS OF NON-SMOKING WOMEN WITH LUNG CANCER AND OF NON-SMOKING CONTROL WOMEN

Diagnostic group	Non-smokers	Ex-smokers	Cigarettes per day (current smokers)				
			1–10	11–20	21–30	31+	Total
Lung cancer	11	6	2	13	4	4	40
Controls	71	22	9	32	6	9	149
RR[1]	1.0	1.8	2.4		3.4		

[1] Relative risk – the ratio of the risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are non-smokers. – X^2 (linear trend) = 6.45, p (2-tail) <0.02.

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It was noted above that the proportion of never-married women is lower among the cases than among the controls, and, since single women have been classified with those whose husbands were non-smokers, the associations in Tables II and III are stronger than would have been observed if concern were limited to ever-married women. In Athens, in the age-groups involved in this study, never-married women tend to have the traditional values and habits associated with singleness in elderly women and for this reason are, we believe, correctly classified in the extreme group of women never having been exposed to a husband's cigarette smoking. However, if the single women are excluded, the association remains significant ($X^2 = 4.6$; $p \simeq 0.03$) and relative risks of 1.5, 2.0 and 3.0 are observed for the three categories of husband's smoking for which relative risks are shown in Table II.

It is, on first consideration, strange that the relative risk associated with passive smoking in this study (2.4 for all categories of smokers combined) is only slightly lower than the figure of 2.9 associated with active smoking by the women themselves. However, the numbers are small and the confidence limits of the latter figure are broad (95%, 1.3-6.8). In the only other controlled study of this matter in Greece (Kanellakis *et al.*, 1976), smokers of less than one pack of cigarettes a day had a 5-fold and smokers of more than one pack per day a 20-fold increase in lung cancer relative to non-smokers. These are the risks appropriately compared with our estimates of 2.4 and 3.4 associated with husband's smoking of similar amounts. Further, active "smoking" does not have the same connotation in men and women. Women smokers tend to smoke less heavily than male smokers but have lower relative risks of lung cancer even for a given level of smoking (Hammond, 1972). The explanation appears to lie in the facts that duration of smoking is an important determinant of risk, women in the current lung cancer ages commenced smoking at a later age than men of similar age and have therefore been smoking for shorter periods, and substantially smaller proportions of women than men inhale (Wald, 1978; Doll *et al.*, 1980). These factors complicate a comparison of the risks associated with active and passive smoking, but at least one of them - the frequency of inhalation - seems likely to operate in favor of a relatively larger effect for passive than for active smoking, other components of the exposure being equal. Finally, it has been observed that smokers tend to clus-

TABLE III

DISTRIBUTION OF NON-SMOKING WOMEN WITH LUNG CANCER AND OF NON-SMOKING CONTROL WOMEN ACCORDING TO THE ESTIMATED TOTAL NUMBER OF CIGARETTES SMOKED BY THEIR HUSBANDS BY THE TIME OF THE INTERVIEW

Diagnostic group	Total number of cigarettes (in thousands)						
	0	1-99	100-199	200-299	300-399	400+	Total
Lung cancer	8	4	6	9	6	7	40
Controls	56	21	26	16	12	18	149
RR[1]	1.0	1.3	2.5		3.0		

[1] See footnote to Table I. X^2 (linear trend) = 6.50, p (2-tail) < 0.02

DISCUSSION

This study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed. Most seriously, the numbers of cases are small. Nevertheless, the association is in the direction expected - if any association were to be expected - and is unlikely to be due to chance. There is a high percentage (35%) of cases lacking cytology, but the association existed both in those with and in those without cytologic diagnosis. That the comparison group was taken from a different hospital from those of the cases may also raise questions. However, the ratio of smokers among the cases themselves to that among the comparison patients is about as expected from previous studies of smoking and lung cancer in women (Hammond, 1966; Doll *et al.*, 1980), and no major demographic difference between cases and controls was found, other than in the proportion of single women. The difference in the proportion of single women is consistent with the hypothesis of a meaningful association between lung cancer risk and husband's smoking, but in any event cannot explain the difference observed within the group of married women.

Against the limitations of the study must be put the fact that the Greek setting provides a somewhat unusual opportunity to investigate this issue. Until about 20 years ago, smoking was unusual among women, whereas it was already quite common among men (Greek Cancer Society, 1978). It is therefore easier to discover an effect of passive smoking among Greek women than among men or women in other Western populations, since in the latter groups the overwhelming effects of active smoking, together with the high correlation between smoking habits of spouses, will confound and conceal the lesser effects of passive smoking.

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ter together socially (Reeder, 1977), and the smoking habits of a woman's husband may be an index of a broader exposure to cigarette smoke than that which emanates from the husband himself.

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Trichopoulos, D., Kalandidi, A. and Sparros, L., "Lung Cancer and Passive Smoking: Conclusions of Greek Study," The Lancet II: 677-678, 1983.

In this letter to the editor, the authors update their conclusions, originally presented in 1981. At this time, the total number of cases was 102, of controls, 251, with 77 cases and 225 controls being nonsmokers. Of these, however, only 38 were married to current smokers. As in the initial report, relative risks of 2.4 and 3.4 were calculated for spousal smoking and were presented without CIs.

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Letters to the Editor

PNEUMOCOCCAL PERITONITIS ASSOCIATED WITH AN IUCD

SIR,—A series of 116 patients at East Birmingham Hospital who had pneumococcal bacteraemia during the years 1974–82 included 5 cases of peritonitis—2 in patients with nephrotic syndrome (a well-known association) and three in women of previous good health who had been fitted with an intrauterine contraceptive device (IUCD).

Case 1.—A 32-year-old woman was admitted to hospital in October, 1978, after 4 days of abdominal pain and distension, with a temperature of 38·5°C and clinical signs of peritonitis. Rectal examination was normal. Abdominal X-rays showed many fluid levels with distended small-bowel loops. A correctly placed IUCD ("Gravigard") was also noted. This had been fitted 18 months previously. A chest X-ray was normal. The clinical diagnosis was invasive salmonellosis; she was given intravenous chloramphenicol and improved. No intestinal pathogens were isolated but blood culture yielded a pure growth of *Streptococcus pneumoniae*. On benzylpenicillin she continued to improve. After a transient fever 2 weeks after admission a chest X-ray was repeated, demonstrating right-lower-lobe consolidation. She recovered completely without further treatment. Her IUCD was removed in August, 1979, when it was described as "unremarkable".

Case 2.—A 46-year-old woman was admitted in March, 1981, after a 5 day history of continuous abdominal pain and watery diarrhoea. Her temperature was 38·2°C and she had clinical signs of peritonitis. Vaginal examination revealed a large tender uterus. Abdominal X-rays showed many fluid levels and a correctly placed IUCD (Lippes loop, fitted in October, 1975). A chest X-ray was normal. High vaginal swabs revealed pus cells and normal commensal flora. She was given gentamicin and metronidazole but did not improve. After 2 days, *Strep pneumoniae* was isolated from blood culture. Benzylpenicillin was given and thereafter she recovered quickly. The IUCD appeared normal when removed 12 days after admission.

Case 3.—A 46-year-old woman with mild mitral stenosis was admitted with a 7 day history of abdominal pain and diarrhoea. She was hypotensive with clinical signs of peritonitis. Laparotomy confirmed peritonitis but did not reveal its cause. However, *Strep pneumoniae* was later grown from both peritoneal fluid and blood. Despite antibiotic treatment acute renal failure and cardiac failure developed and she died 8 days after admission. Necropsy revealed a bicornuate uterus. In one horn there was a 'Dalkon' shield IUCD adjacent to a small infarcted fibroid. This IUCD, a radiolucent type, had been fitted at least 4 years previously. Although there was no microscopic evidence of endometritis, bilateral salpingitis was present. There was no evidence of pneumonia.

In no case was *Strep pneumoniae* isolated from the genital tract, and only in case 2 was there evidence of metritis. Despite this, it is difficult to discount the presence of the IUCD. Only 6% of British women aged 30–50 use an IUCD.[1] If all women in this age group are equally at risk of pneumococcal peritonitis the probability of all three cases in our series being in women using an IUCD is 0·000216. This indicates a highly significant association between IUCD usage and pneumococcal peritonitis.

We know of only 1 previous case-report of pneumococcal peritonitis in a woman using an IUCD (a Lippes loop fitted 2 years before the infection),[2] but of several cases of pneumococcal endometritis and peritonitis during pregnancy and the puerperium.[3,4] The pneumococcus is often found in the oropharynx[5] but not in the adult female genital tract.[6] An IUCD or placental tissue could provide a sanctuary for pneumococci borne in the blood from the oropharynx, or the lung, before invasion of the peritoneal cavity.

Pneumococcal peritonitis associated with an IUCD is clearly very rare. Failure to treat it promptly could, however, have tragic results. We suggest that any woman using an IUCD who presents with peritonitis without an obvious cause should be given antibiotics with activity against *Strep pneumoniae* (eg, a penicillin or cephalosporin). This advice might apply particularly for women over 30 whose IUCD had been fitted months or years earlier.

Department of Medical Microbiology, Medical School, University of Birmingham, Birmingham B15 2TJ — L. D. GRUER

Public Health Laboratory, East Birmingham Hospital — K. E. COLLINGHAM

Department of Pathology, East Birmingham Hospital — C. W. EDWARDS

LUNG CANCER AND PASSIVE SMOKING: CONCLUSION OF GREEK STUDY

SIR,—The notion that passive smoking may increase the risk of lung cancer has been supported by the results of two epidemiological studies specifically designed to explore the issue,[7,8] while a third[9] revealed a positive but not significant and dose-unrelated association. Positive results have also been reported from Pennsylvania[10] and Germany,[11] but no association was found in a study in Hong Kong.[12] The association has been considered credible, on empirical and theoretical grounds,[13] but a *Lancet* editorial[13] has summed up the situation by saying that the message of these studies "is not that epidemiologists and others have proved an association ... but that getting proof may not be as difficult as it once seemed".

Most of the controversy was generated by the simultaneous publication of the Greek[7] and Japanese[8] studies. Both have been criticised, and Hirayama has responded for the study in Japan.[14-16] The Greek study was criticised (by ourselves[7] and others) because of the small number of subjects, because several tumours lacked histological confirmation, and because controls and cases were from different hospitals. The Greek study has now been concluded (in A. K.'s professorial thesis, University of Athens). Although doubt must remain about the histological evidence and hospital differences there are now twice as many cases and 50% more controls; the results remain substantially the same.

102 women with a final diagnosis of lung cancer other than adenocarcinoma or terminal bronchial carcinoma, admitted to the three largest chest cancer hospitals in Athens, were interviewed between September, 1976, and December, 1982, together with 251 controls in the Hospital for Orthopaedic Disorders, Athens, from the same area of Athens as the cases. Cases and controls were interviewed by the same physician. 77 cases and 225 controls were non-smokers, and their demographic and socioeconomic profiles were very similar. Husbands who had stopped smoking 5–20 years before the interview were classified as ex-smokers, those who had stopped smoking within 5 years of the interview were considered as current smokers, and those who had stopped smoking more than 20 years previously were classified as non-smokers. Being never married, a widow, or a divorcee was considered as equivalent to marriage to a non-smoker or an ex-smoker, depending on the years elapsed since the event.

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SMOKING HABITS OF HUSBANDS OF NON SMOKING WOMEN WITH LUNG CANCER AND OF NON SMOKING CONTROL WOMEN

Group	Non-smokers	Ex-smokers	Cigarettes per day (current smokers)				Total
			1–10	11–20	21–30	31+	
Lung cancer	24	15	2	22	7	7	77
Controls	109	35	16	40	8	17	225
RR*	1·0	1·9	2·4		3·4		..

*Relative risk = ratio of risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are non-smokers. χ² (linear trend) = 7, p (two-tail) about 0·01

The table increases the credibility of the hypothesis implicating passive smoking as a factor in lung cancer. Given the small size of the relative risk and the many potential sources of bias, no single study will be able to provide convincing evidence for or against this hypothesis; only the convergence of results from different studies in different populations will permit a reasonably sound conclusion. We consider the Athens study a step in this direction.

This study was supported principally by the Greek Ministry of Health

Department of Hygiene and Epidemiology, University of Athens, Athens 11527, Greece, and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA

DIMITRIOS TRICHOPOULOS
ANNA KALANDIDI
LOUKAS SPARROS

GLASGOW COMA SCALE: TO SUM OR NOT TO SUM?

SIR,—The method for assessing patients with impaired consciousness that we described almost a decade ago[1] has been widely accepted, and in many centres the eye, verbal, and motor components are summed.[2] Totals up to 8 relate to patients in coma with no eye opening or verbal responses, reflecting changes in motor response, scores from 9 to 15 depend more upon eye opening and verbal responses. Janine Jagger and her colleagues (July 9, p 97) doubt if eye and verbal responses add predictive information. They studied the short-term outcome in head-injured patients assessed on admission only. Not surprisingly, they found the motor responses to be most informative; patients who, on admission, show eye opening and comprehensible verbal responses ought not to die. Death can be expected only amongst patients already in coma due to severe established brain damage. Such patients would have no eye opening and no comprehensible verbal responses so that their coma score would depend upon the motor response.

Changes in the eye and verbal responses, and thus higher overall scores, are useful in discriminating between patients with less severe impairment of consciousness. Although these patients would be expected to survive, this may be with differing degrees of disability. The Charlottesville group themselves found that increasing scores in the 9–15 range (reflecting improving eye and verbal performances) are associated with a doubling of the rate of good recovery in survivors of head injury.[3] Furthermore, correlations have been established across the whole range of the coma score with cerebral metabolic rate for oxygen,[4] evoked potential studies,[5] and biochemical indices of brain damage.[6]

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5. Lindsay KWL, Carlin J, Kennedy I, Fry J, McInnes A, Teasdale GM. Evoked potentials in severe head injury: Analysis and relation to outcome. *J Neurol Neurosurg Psychiatry* 1981; 44: 796–802.
6. Bailey RAE, Ward AE Jr. Enzymatic changes in serum and cerebrospinal fluid in neurological injury. *J Neurosurg* 1983; 58: 27–37.

Head-injured patients may change rapidly after admission, and the eye and verbal responses are useful in assessing improvement or deterioration to show whether a patient is in coma and how long he remains comatose. Scores obtained during the first few days after admission reveal much more about prognosis than do admission scores.

The analysis used by the Charlottesville group is not well suited to comparing the relative predictive power of different clinical features and can exaggerate minor differences. Moreover, they included information about pupil responses and about a haematoma which could not have been known at the time of admission. Yet they have previously demonstrated correlations between higher coma scores and decreasing frequency of abnormal pupil responses and CT scan abnormalities in moderately injured patients. Because of this, the inclusion of these features may have masked the information provided by the eye and verbal responses. Their analysis should have been restricted to the three aspects of the coma scale. They would then have found[2] that knowledge of the eye and verbal responses in addition to the motor response, does convey extra information, whether the three responses are considered separately or summed.

Although we cannot accept the Charlottesville group's reservations about the value of the eye and verbal components there are limitations inherent in the summation of the three responses. This step assumes an equal weighting for the three responses. More importantly, the information conveyed by the coma score is less than that contained in the three responses separately.[2,7] This is because the same score may be made up in different ways. Indeed, in Glasgow patients under treatment are always described by the three separate responses and never by the total. The total score is merely a convenient method for summarising data, especially for a series of patients. Therefore, while we do not favour its use in day-to-day clinical practice, we find no reason to doubt that it will continue to be used widely in the analysis and reporting of a series of patients with head injuries or other forms of acute brain damage.

Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF

GRAHAM TEASDALE
BRYAN JENNETT
LILIAN MURRAY
GORDON MURRAY

CULTURED EPIDERMAL CELLS AND BURNS

SIR,—We read the article by Dr Hefton and colleagues (Aug 20, p 428) with interest because for some time we have been studying both human epidermal cell culture and methods for stimulating the re-epithelialisation of non-healing ulcers. Before those caring for burns patients rush out to buy an epidermal cell culture kit a note of caution should be sounded. It took many years before human epidermal cells could be cultivated regularly in vitro. The techniques require considerable skill and experience to have consistent success even with a feeder layer of mouse derived 3T3 cells: to grow cells from cadaver skin (how long after death we are not told) without a feeder layer is praiseworthy but not within the grasp of many other laboratories.

With the system used by Hefton et al, based on the studies of Eisinger et al,[8] there does not appear to be an increase in the number of epidermal cells. The total number of cells in culture after 25 days is less than the number of cells seeded at day 0 (see fig 2 in Eisinger et al). This would imply that the system as a whole has the disadvantage that an area of cadaver skin equal in area to the site to be covered would be required for grafting. On the other hand the 3T3 fibroblast system used by O'Connor et al[9] is capable of a considerable increase in the number of cells in vitro. Unless Hefton

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Garfinkel, L., "Time Trends in Lung Cancer Mortality Among Nonsmokers and a Note on Passive Smoking," Journal of the National Cancer Institute 66: 1061-1066, 1981.

This paper reports on a subset of the American Cancer Society's large prospective study. Data, including husband's smoking status, were available for 176,739 women.

For women whose husbands smoked <20 cigarettes/day, a mortality ratio of 1.27 (95% CI 0.85-1.89) was calculated; for those whose husbands smoked ≥20 cigarettes/day, the reported mortality ratio was 1.10 (95% CI 0.77-1.61).

A matched-groups analysis was carried out to take into account potential confounding factors such as age, race, highest educational status of husband or wife, residence and husband's occupational exposure to dust, fumes or vapors. The mortality ratios for spousal smoking generated by this analysis were not statistically significant.

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Time Trends in Lung Cancer Mortality Among Nonsmokers and a Note on Passive Smoking [1]

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Lawrence Garfinkel, *M.A.* [2,3]

ABSTRACT—Lung cancer mortality rates were computed for nonsmokers in the American Cancer Society's prospective study for three 4-year periods from 1960 to 1972 and in the Dorn study of veterans for three 5-year periods from 1954 to 1969. There was no evidence of any trend in these rates by 5-year age groups or for the total groups. No time trend was observed in nonsmokers for cancers of other selected sites except for a decrease in cancer of the uterus. Compared to nonsmoking women married to nonsmoking husbands, nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer.—JNCI 1981; 66:1061-1066.

Mortality rates from lung cancer in men in the United States have been rising steadily since 1930 (the first year these cancers were classified separately) and in women since the mid-1960's. It has generally been accepted that the major reason for the increase has been the cigarette smoking patterns which began in young men around World War I and in young women in the 1930's and 1940's. A large body of evidence from epidemiologic and pathologic studies on smokers confirms this conclusion (*1*). A recent estimate of the percentage of cancers attributable to smoking in men was 34.5% for total cancers and 82.8% for lung cancer. In women the comparable percentages were 5.4 and 43.1% (*2*). This analysis was based on data from the large epidemiologic study of the ACS and covered the period 1967-71. It was based on a number of assumptions that would give slightly different figures if the smoking distributions in the study population differed from those of the general population or if smoking distributions changed in the late 1970's compared to the late 1960's (as they indeed have in women).

There has been a suggestion, however, that the lung cancer trend in nonsmokers has also increased in the United States over the years. Enstrom (*3*) stated that "a more complete understanding of lung cancer etiology is needed." This analysis indicated a large relative increase in lung cancer mortality in nonsmokers in both white men and white women between 1914 and 1975 on the basis of an interpretation of data in samples of national mortality statistics and several epidemiologic studies in different periods of time (*3*). Enstrom recognized that most of the increase occurred between a 1914 survey of death registration areas in 24 states and national mortality statistics reported in 1935 and that most of that increase was probably attributable to incompleteness of reporting lung cancer and to changes in diagnostic criteria.

Nevertheless, the possibility exists that lung cancer is increasing in nonsmokers who have had increasing exposure to other factors—occupational exposures, general air pollution, and perhaps even to passive smoking (inhaling the smoke from smokers). Even if these factors were related to the alleged increase in lung cancer, they could have had only minimal effect on the upward trend for lung cancer in men, since the mortality rates among smokers and nonsmokers differ so greatly. Moreover, in the last 50 years and until recently, most men had a history of cigarette smoking. Among women lung cancer rates remained low up to about 1960. Since then, there has been a threefold increase in rates attributable in large part to the changes in smoking patterns among women during the preceding two or three decades.

In this paper, information is provided on trends for lung cancer (and cancers of several other sites) in nonsmokers over a 12-year period (1960-72) from data in the prospective study of the ACS. In addition, data for nonsmokers from the Dorn study of veterans for the years 1955-69 are given. While such data do not provide evidence over a very long time span, they are based on the two largest prospective studies in the United States and cover a 17½-year period from 1955 to 1972.

MATERIALS AND METHODS

Procedures in the collection of data in the prospective study of the ACS have been presented in a number of publications (*4-6*). There were 94,000 male and 375,000 female nonsmokers at the start of the study. In the ACS study, a "nonsmoker" is one who reported he or she had never smoked or smoked only occasionally but had never smoked regularly. Classification was made as of the start of the study, and very few nonsmokers reported that they started to smoke on any of four later questionnaires.

Enrollment of subjects in the ACS study began in October 1959 and extended through March 1960. Follow-up was complete for 98.4% of all subjects through June 1971 and 92.8% complete for the 12th year of the study. Deaths were reported by the ACS volunteers, and death certificates were obtained from state health de-

Abbreviation used: ACS = American Cancer Society.

[1] Received October 23, 1980; accepted January 26, 1981.

[2] Department of Epidemiology and Statistics, American Cancer Society, 777 Third Ave., New York, N.Y. 10017.

[3] I thank Eugene Rogot for supplying the data for the Dorn study of veterans and Henry Vasquez and Linda Merlino for assisting in the processing of the data in this study.

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partments. Mortality data for this analysis begin with observation starting on July 1, 1960. Data are presented for three 4-year periods: period 1, July 1, 1960, through June 30, 1964; period 2, July 1, 1964, through June 30, 1968; and period 3, July 1, 1968, through June 30, 1972. Person-years of observation in nonsmokers and deaths at single years of attained ages 35–89 years were computed and combined by 5-year attained age groups.

In the Dorn study of veterans, questionnaires were mailed starting in January 1954 to 293,000 veterans holding U.S. Government life insurance. About 65% of the questionnaires were received over a period of several months. In January 1957 a second questionnaire was mailed to those not responding to the first mailing and the replies raised the total to 85% (7). About 54,000 of those who replied were nonsmokers. The same classification of nonsmokers was used in this study as was used for the ACS study. Person-years of observation and mortality by single years of attained age were computed starting with January 1, 1955, for the responders to the first mailing and starting with January 1, 1958, for the responders to the second mailing. Death certificates were supplied to the Veterans' Administration in support of insurance claims through 1962. For the period 1962–69, death certificates were obtained through field work at health departments by ACS personnel (*8*).

Death rates by 5-year age groups were adjusted to the distribution of the stationary population ($_5L_x$) of white men and white women of ages 35 years and over in the abridged life tables for the U.S. population in 1965 (*9*). Differences in death rates for periods 1 and 2 and periods 1 and 3 were tested for significance at the $P<0.05$ level by the Mantel-Haenszel procedure (*10*).

RESULTS

Time Trends in Lung Cancer Mortality Among Nonsmokers

Table 1 shows the 5-year attained age death rates for lung cancer among nonsmokers in three periods of time. The table includes men and women in the ACS study and men in the Dorn study of veterans. There were 195 deaths from lung cancer among male nonsmokers and 564 deaths from lung cancer among female nonsmokers in the ACS study during the 12-year period. There were 168 deaths from lung cancer among nonsmokers in the 15-year period in the Dorn study of veterans. Some of the rates computed for 5-

TABLE 1.—*Death rates from lung cancer per 100,000 person-years among nonsmokers, ages 35–89 years, by time period: ACS prospective study and the Dorn study of veterans*

Attained age group, yr[a]	ACS prospective study[b]			Dorn's study of veterans[b]		
	Period 1: July 1960–June 1964	Period 2: July 1964–June 1968	Period 3: July 1968–June 1972	Period 1: Jan. 1955–Dec. 1959	Period 2: Jan. 1960–Dec. 1964	Period 3: Jan. 1965–Dec. 1969
Males						
35–39	—	—	—	—	—	—
40–44	—	(8.7)	(14.3)	—	—	(103.5)
45–49	(4.0)	(5.1)	—	—	—	(8.6)
50–54	(5.3)	8.8	(8.8)	—	—	—
55–59	10.5	11.6	8.3	(12.0)	—	—
60–64	17.0	17.3	17.5	11.2	(10.7)	(48.0)
65–69	18.6	29.4	34.3	25.1	16.9	43.5
70–74	32.3	26.4	19.2	39.9	40.5	38.2
75–79	32.7	41.5	58.6	(37.8)	(15.0)	47.2
80–84	(47.9)	106.8	51.9	—	(200.6)	(20.6)
85–89	61.8	152.7	(69.9)	(595.2)	—	—
No. of deaths	52	74	69	38	52	78
Age-standardized death rate	12.5	18.5	15.8	18.9	13.4	19.6
Females						
35–39	—	—	—			
40–44	—	(3.5)	(3.5)			
45–49	5.9	(3.3)	(1.6)			
50–54	5.2	7.7	(3.0)			
55–59	7.4	8.0	5.8			
60–64	14.0	12.3	14.5			
65–69	15.6	15.2	17.7			
70–74	19.4	21.1	22.0			
75–79	37.3	30.5	36.3			
80–84	51.5	45.1	40.8			
85–89	53.4	44.5	59.5			
No. of deaths	175	184	205			
Age-standardized death rate	13.8	12.9	13.1			

[a] Some 5-yr age groups were combined in the standardization of rates to avoid 0 cases in these groups.
[b] *Numbers in parentheses* indicate <5 deaths in group.

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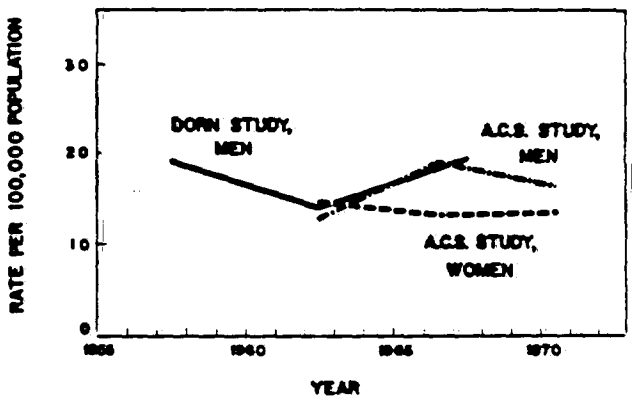
year age groups were small and subject to considerable sampling variation. There was no appearance of any consistent increase in the lung cancer death rate among nonsmokers with time by 5-year age groups. The age-standardized rates for males shown in table 1 and in text-figure 1 showed no trend. The rates for women were based on many more cases, and the age-standardized rate was virtually the same in all three periods. The differences in rates between periods 1 and 2 and periods 1 and 3 were not statistically significant in both the ACS study and the Dorn study of veterans. The analysis was based on the underlying cause of death on death certificates. The death rates for the three periods were also standardized to the distribution of the stationary population of white men and women combined, of ages 35 years and over, in the abridged life table for the U.S. population in 1965. This standardization raised the rates for males slightly and decreased the rates for females slightly, but it changed the pattern of the trends very little.

An attempt was made in the first 6 years of follow-up in the ACS study to obtain confirmation of diagnosis for all cases with cancer from physicians who signed the death certificates or from hospitals in which death occurred. Information was received confirming the primary site of cancer in 78% of the cases, and microscopic confirmation was obtained in 69% of the cases in the first 6 years (*6*).

Table 2 shows a comparison of the death certificate diagnosis and the final diagnosis from the medical report. Among nonsmoking men, 74 were reported to have died of lung cancer according to the death certificates. Six of these (8.1%) were reported to have died of cancer of another site on the final report. However, 9 (0.8%) of the deaths reported as being due to cancer of a site other than lung on death certificates proved to be due to lung cancer on the final report. Thus among nonsmoking men there were 74 deaths from lung cancer reported on death certificates and 77 deaths from lung cancer according to the final medical report.



TEXT-FIGURE 1.—Lung cancer mortality rates in three 4-yr periods for nonsmokers in the ACS prospective study and for nonsmokers in three 5-yr periods in the Dorn study of veterans.

TABLE 2.—*Lung cancer deaths among nonsmokers in first 6 years of study on death certificates and on final reports*

Final report diagnosis	Death certificate diagnosis			
	Lung cancer		Other cancer	
	No.	Percent	No.	Percent
Males				
Lung cancer	68	91.9	9	0.8
Other cancer	6	8.1	1,153	99.2
Total	74	100.0	1,162	100.0
Females				
Lung cancer	169	83.3	10	0.2
Other cancer	34	16.7	5,160	99.8
Total	203	100.0	5,170	100.0

In women the picture was somewhat different. Two hundred and three cases of lung cancer among nonsmokers were reported to be lung cancers on death certificates, and 34 (16.7%) were reported to be cancers of other sites on the final medical report. A smaller number, 10 (0.8%), of those cancers that were reported as being of a site other than the lung on death certificates were reported to be lung cancers on the final report. Thus on death certificate reports, 203 nonsmoking women were reported to have died of lung cancer in the first 6 years. On the final report, 179 (a decrease of 11.8%) were reported to have died of lung cancer. About one-third of the 34 females whose causes of death were attributed to lung cancer on the death certificates and changed on medical confirmation died from breast cancers. However, breast cancer was underdiagnosed on death certificates in nonsmoking women. There were 1,310 breast cancers reported on death certificates in the first 6 years of the study and 1,371 on the final report.

Table 3 shows the age-standardized rates for total mortality for all cancers and for cancers of selected sites among nonsmokers in the three time periods. Overall mortality in men decreased 3% from period 1 to 3. This slight difference was statistically significant at the $P<0.05$ level because of the large number of deaths involved. None of the differences in total cancer or in cancers of other sites in men in table 3 between periods 1 and 2 and periods 1 and 3 were statistically significant. Women had an 8% decrease in total death rates between periods 1 and 3. The difference in rates was statistically significant. The decreases in total cancer and uterine cancer between periods 1 and 2 and periods 1 and 3 were statistically significant. None of the differences for cancers of other sites were statistically significant except for the 29% decrease in cancers of the buccal cavity, pharynx, larynx, and esophagus between periods 1 and 3.

Passive Smoking

A number of studies have established that nonsmokers exposed to smoke from cigarettes in a poorly

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TABLE 3.—*Trends in mortality rates from cancers of selected sites in three time periods for nonsmokers: ACS prospective study, 1960–7*

Parameter	No. of deaths	Period 1: July 1960–June 1964	Period 2: July 1964–June 1968	Period 3: July 1968–June 1972
Males				
Total deaths	19,805	1,608.7	1,588.6	1,559.9
Total cancers	3,151	247.8	252.4	251.6
Cancers of buccal cavity, pharynx, larynx, and esophagus	62	6.86	6.79	5.46
Cancer of colon–rectum	636	51.9	45.0	50.4
Cancer of pancreas	199	15.0	17.6	14.0
Cancer of prostate gland	573	69.5	63.1	59.6
Females				
Total deaths	52,965	1,494.5	1,485.8	1,374.2
Total cancers	13,275	317.9	304.6	298.1
Cancers of buccal cavity, pharynx, larynx, and esophagus	159	4.88	4.21	3.48
Cancer of colon–rectum	2,429	58.0	59.8	56.7
Cancer of pancreas	688	17.4	16.2	14.8
Cancer of breast	3,186	69.3	68.0	75.0
Cancer of uterus	833	22.1	18.4	15.0

ventilated room will show increased levels of carbon monoxide in their blood. These higher levels of carbon monoxide can result in deterioration of psychomotor performance. Many nonsmokers have acute eye and throat irritation responses in the environment of cigarette smokers (*11*). One paper reported changes in lung function tests in people classified as passive smokers compared to nonsmokers, and these changes were interpreted as demonstrating a greater reduction in the function of small airways (*12*). Hirayama (*13*) reported lung cancer mortality ratios in Japan ranging up to 2:1 in nonsmoking women with husbands who smoked 20 or more cigarettes a day compared to nonsmoking women with nonsmoking husbands. Trichopolous et al. (*14*) reported similar findings in a case-control study in Greece.

A similar analysis was made of nonsmokers in the ACS study, even though classifying nonsmoking women on the basis of the smoking habits of their husbands is not an accurate measure of their degree of passive smoking. Moreover, exposures in Japan and Greece may be very different than they are in the United States. Lung cancer mortality among persons who were married to cigarette smokers was compared with the mortality among those married to nonsmokers.

A total of 176,739 nonsmoking women were identified who were married *a*) to men who never smoked, *b*) to men who currently smoked cigarettes regularly but less than 20 cigarettes a day, and *c*) to men who currently smoked 20 or more cigarettes a day. Most husbands had smoked for 20 or more years before the study began, and presumably their wives were more likely to have been passive smokers than were the women married to nonsmokers. Twenty-eight percent of the husbands of nonsmoking women were nonsmokers compared to 21% of men in the total study population. Table 4 shows the results of this analysis. Expected numbers of deaths were based on the lung cancer rates for the 12-year period (1960–72), by 5-year age groups of the women with nonsmoking husbands. No attempt was made in this first analysis to adjust for other possible confounding factors. The observed versus expected lung cancer mortality ratio for women whose husbands smoked less than 20 cigarettes a day was 1.27; for those whose husbands smoked 20 or more cigarettes a day, it was 1.10. Neither of these differences was statistically significant at $P<0.05$ by the Mantel-Haenszel procedure.

A separate matched-groups analysis was made of the lung cancer deaths among the same 3 groups of women to eliminate the possible effects of potential confounding factors. The women in the 3 groups were matched by age (5-yr age groups), race (white, nonwhite), highest educational status of husband or wife (not a high school graduate, high school graduate, or higher), residence (rural, not rural), and husband occupationally exposed to dust, fumes, or vapors (yes or no). The analysis was restricted to nonsmoking women who were not sick and who had no serious disease at the start of the study. "Adjusted" numbers of deaths for each matched diad were computed, as described in other publications (*15*, *16*). In this pro-

TABLE 4.—*Observed versus expected[a] lung cancer deaths among nonsmoking women with cigarette smoking husbands: ACS study, 1960–72[b]*

Parameter	Husband did not smoke	Husband smoked <20 cigarettes/day	Husband smoked ≥20 cigarettes/day
Observed deaths	65	39	49
Expected deaths	65.00	30.67	44.67
Mortality ratio	1.00	1.27	1.10

[a] Expected deaths are based on the lung cancer rates by 5-yr age groups in women with nonsmoking husbands applied to the person-years of women with smoking husbands.

[b] The 95% confidence limit for women with husbands smoking <20 cigarettes/day was 0.85, 1.89; for women with husbands smoking ≥20 cigarettes/day, it was 0.77, 1.61.

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TABLE 5.—*Matched group study: Adjusted[a] lung cancer deaths among women with nonsmoking husbands matched[b] with women with smoking husbands*

Group	No. of adjusted lung cancer deaths	Ratio	P[c]
Nonsmoking husband	25.6	1.00	
Husband smoked <20 cigarettes/day	35.0	1.37	NS
Nonsmoking husband	34.5	1.00	
Husband smoked ≥20 cigarettes/day	35.8	1.04	NS

[a] See text for definition of adjusted deaths.
[b] Matched on the basis of *a*) wife's 5-yr age group, *b*) husband's occupational exposure, *c*) highest educational level of husband or wife, *d*) race, *e*) urban–rural residence, and *f*) absence of serious disease at the start of the study.
[c] NS = not significant.

cedure women whose husbands never smoked were compared to women from each of the 2 groups in which the husband smoked cigarettes. The number of lung cancer deaths in each matched diad was adjusted to the proportion of persons for each group and summed over all groups to give an "adjusted" number of lung cancer deaths. Variances were computed for each of the matched groups and summed over all matched groups, and probabilities were computed under the null hypothesis of observing no differences. The results of this analysis are shown in table 5. The ratio of adjusted lung cancer deaths in women whose husbands smoked less than 20 cigarettes a day to those in women whose husbands never smoked was 1.37. The comparable ratio for women whose husbands smoked 20 or more cigarettes a day was 1.04. None of these differences were statistically significant ($P>0.05$).

DISCUSSION

Data from the two prospective studies reported in this paper indicate that the age-adjusted mortality rate for lung cancer in nonsmoking men 35–89 years old was between 12 and 19/100,000 in the 1950's and 1960's. The observed rate for women was about 13/100,000. The rate may actually be about 10% less because lung cancer in nonsmoking women may be over-reported on death certificates. The lung cancer rates shown in table 1 may be slightly different from those shown in other publications because different years, age groups, or methods of standardization were employed.

The rates for male and female nonsmokers by age group in this analysis were in about the same range as that of the 1958 rates for nonsmokers in Haenszel's report of a 10% sample of death certificates in the United States (*17, 18*). The 1966–68 estimates derived by Enstrom from several sources are not directly comparable because of a different classification of nonsmokers ("never smoked cigarettes") (*3*). The male rates in the period 1968–72 are about one-half those reported by Enstrom for active Mormons in 1968–75 (*19*). Enstrom defined active Mormons as a cohort that can be considered "almost entirely as white males who never smoked," and he used this cohort to serve as the nonsmoker lung cancer rates in the 1968–75 period "in lieu of recent national mortality data on nonsmokers." The mortality rates for lung cancer in both male and female nonsmokers by 5-year age groups showed no consistent trends over the period in this study.

Long-term effects of passive smoking are difficult to establish because of the problems in classification. It may be misleading to classify a women as a passive smoker or not on the basis of her husband's smoking habit. Wives of nonsmokers may be more exposed to cigarette smoke of others than wives of cigarette-smoking men; wives of smokers may be very little exposed to the cigarette smoke from their husbands or others. In addition, 13% of the women nonsmokers who died of lung cancer in the ACS study reported that they were previously married, and the classification of their exposure to their husbands' smoking may not be pertinent.

In autopsy studies of cigarette smokers, there was a dose-related spectrum of histologic findings, including basal cell hyperplasia, metaplasia, and cells with atypical nuclei in the mucosa of the tracheobronchial tree that may lead to invasive carcinoma. In contrast, advanced histologic changes in specimens from the tracheobronchial tree, such as lesions with six or more cell rows, lesions having 50% or more cells with atypical nuclei, and carcinoma in situ, were found in less than 0.1% of the slides of nonsmokers (*20*). Since there is such little variation in the appearance of these histologic changes in nonsmokers of different age, sex, and residence, it seems doubtful that those nonsmokers who had been heavily exposed to cigarette smoke from others in their lives could have had many more precursor lesions for the development of lung cancer than nonsmokers not so exposed. Therefore, there is evidence from these studies that passive smoking cannot play more than a very small role in the development of lung cancer.

Mortality ratios for male smokers of less than 10 cigarettes a day compared to those of nonsmokers range from 2 to 1 in Japan to nearly 5 to 1 in the United States. Mortality ratios in women are even lower. It appears unlikely on a biologic basis, therefore, that wives with husbands who smoke 20 or more cigarettes a day can have mortality ratios that approach those of regular cigarette smokers.

To obtain data on passive smoking in nonsmoking women, an epidemiologic study should be specifically designed to measure their exposure as accurately as possible. This is very difficult to do. Neither the Japanese study nor the ACS study was designed to obtain definitive information on passive smoking.

Data for lung cancer risks in occupationally exposed nonsmokers compared to nonexposed nonsmokers are

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not very extensive. One study showed an increased risk in heavily exposed asbestos workers on the basis of a small number of cases (*21*).

It would be interesting to continue studies of lung cancer trends in nonsmokers over a long period of time, but the major public health problem in lung cancer is with cigarette smokers. Cigarette smokers who are occupationally exposed to asbestos have a greatly elevated risk compared to the risk among cigarette smokers not so exposed (*21*). Lung cancer rates are rising at an alarming rate in women who smoke cigarettes. Educational efforts should focus on smoking-cessation programs for these groups and particularly on persuading young people not to start. Even if the estimates from this analysis are in error and there was a slight increase in lung cancer trends in nonsmokers, it did not appear to be an important problem in the overall picture for the time period of this study.

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Chan, W.C. and Fung, S.C., "Lung Cancer in Non-Smokers in Hong Kong," Cancer Campaign Vol. 6, Cancer Epidemiology, ed. E. Grundmann (Stuttgart: Gustav Fischer Verlag, 1982): 199-202.

This case-control study (84 female non-smokers and 139 controls) examined spousal smoking habits and cooking practices, including types of fuel used. About 82% of the cases were histologically verified.

Relative risks were not presented in the paper. The authors wrote that "there are less passive smokers among patients than the controls" and that "[t]here appears [sic] to be less people [cases] who never cook with kerosene comparing to the control [sic]." The authors concluded that diet might be a future avenue for research.

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

E. Grundmann (ed.): Cancer Campaign, Vol. 6, Cancer Epidemiology
Gustav Fischer Verlag · Stuttgart · New York · 1982

Lung Cancer in Non-Smokers in Hong Kong

W. C. CHAN and S. C. FUNG

Introduction

Bronchial cancer is an important health problem in Hong Kong causing an increasing number of deaths annually. The increase is particularly rapid among men. The death toll increased 50% (802–1217) between 1976–1980. The increase among women was slight (532–581) (Hong Kong, 1980).

Material and Method

In a recent survey of bronchial cancer (CHAN et al., 1979), among 208 male patients only 2 were non-smokers and among 189 female patients 84 were non-smokers. These form the subjects of this investigation. Matched controls were selected from orthopaedic patients.

All patients and controls were interviewed and questions asked about smoking habit of their spouses and their cooking habits, including the types of fuel used. Histological diagnoses of the tumours were obtained.

Results

The age distributions of the non-smoker patients and of the matched controls are shown in *Table 1*. The highest incidence is in the group above 70.

The histological types of the non-smoker's cancers are shown in *Table 2*. It can be seen that adenocarcinoma is the prevalent type. The two male cases are too few to be significant. In a previous study (CHAN and MACLENNAN, 1977) this histological type was also high among males although not as high as among females where it was 54.3% among 277 cases.

In *Table 3*, it is seen that there are less passive smokers among patients than the controls; and more non-smoking patients have non-smoking spouses. This finding is at variance with that of Dr. HIRAYAMA's (1981). He found that mortality from lung cancer of non-smoking women exposed to cigarette smoke of their husbands was increased two folds. The histological types of their cancers were not given. The present group is of course very small in comparison to Dr. HIRAYAMA's material.

The cooking habits of non-smoking women are shown in *Table 4*.

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Table 1: Age Distribution of *Non-smokers* in a Lung Cancer Case Control Study.

Age Group	Male		Female	
	Case	Control	Case	Control
39		6	6	7
40–49		6	13	21
50–59	1	3	19	42
60–69	1	7	19	30
70 –		8	27	39
	2	30	84	139

Table 2: Cell Types of Non-smokers' Lung Cancer Cases.

Cell type	Male	Female
Squamous or epidermoid	1	15
Small cell anaplastic	1	4
Adenocarcinoma		38
Large cell		2
Others and unspecified		10
No histological verification		15
	2	84

Table 3: Number of Passive Smokers among Non-smoking Female Lung Cancer Patients.

	Case	Control
Passive smoker	34 (40.5%)	66 (47.5%)
Non-passive smoker	50 (59.5%)	73 (52.5%)
	84	139

Table 4: Female Non-smokers' Cooking Habits.

	Total	Never cook	Never cook with Kerosene	Never cook with Kerosene or gas
		No.	No.	No.
Case	84	15 (22.4%)	23 (27.4%)	18 (21.4%)
Control	139	29 (20%)	56 (40.3%)	43 (30.0%)

22.4% claimed they never cooked, 27.4% never cooked with kerosene, and 21.4% never cooked with kerosene or gas. There appears to be less people who never cook with kerosene comparing to the control. The difference is found to be insignificant when non-smoking controls were considered. ($X^2 = 1.92$; $0.1 < P < 0.2$).

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Discussion

The interests of this study are:

1. The high incidence rate of female cancer among Southern Chinese (mainly Cantonese women). *Table 5* shows the high proportion of Cantonese. This feature has been reported from Singapore, San Francisco and Hawaii.
2. The high proportion of non-smoker cancer among women.
3. The high proportion of adenocarcinoma in this region and particularly in non-smoker cancer of females.

Table 5: Ethnic Groups of *Non-smoking Female Lung Cancer Patients*, Controls an Hong Kong General Femak Population.

	Case	Control	Hong Kong General Population
Cantonese	68 (81%)	97 (70%)	75.7%
Chiu Chau	5 (6%)	14 (10%)	9.3%
Elsewhere in Kwangtung Province	6 (7%)	7 (5%)	6%
Elsewhere in China and others	5 (6%)	21 (15%)	9%
	84	139	100%

The aetiology of the adenocarcinoma among non-smokers has been the subject of speculation. In the present survey no conclusion can be made on the part played by the cooking habit. The association of carcinoma with tuberculosis was postulated by STEINITZ (1972). MOK et al. (1978) recently studied the association of active tuberculosis and lung cancer. They concluded that there was no causal relationship as both were quite common diseases and chance association was quite probable.

The high incidence of female cancer, particularly adenocarcinoma, among Southern Chinese awaits further elucidation.

There may be a common factor in this region for the high incidence of adenocarcinoma both in men and women. As it is not connected with cooking and smoking, the dietary habit has to be further studied. In an experimental study, FONG and CHAN (1977) produced adenocarcinoma of lung in the rats by feeding them nitrite and aminopyrine, two precursors of dimethyl-nitrosamine. It is possible that precursors may occur in the Cantonese diet which lead to in vivo nitrosamine formation. In the Cantonese diet, large amounts of green vegetables may be present. The possibility of a high nitrite/nitrate content may account for the high incidence of lung cancer independent of cigarette smoking and air pollution. The two latter factors are supposed to lead to squamous carcinoma and small cell carcinoma. Investigation is being undertaken to estimate the nitrate content of vegetables in the South. Preliminary results show a high nitrate content about 4 times that of lettuce from California. A report will be published later (FONG, 1981, personal communication).

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Authors' addresses:

W.C. Chan, M.B., B.S., (H.K.), Ph.D. (London), F.R.C. Path., Consultant Pathologist, St. Teresa's Hospital, Kowloon, Hong Kong.

S.C. Fung, Research Fellow, Department of Community Medicine, University of Hong Kong, Hong Kong.

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Correa, P., Pickle, L.W, Fontham, E., Lin, Y. and Haenszel, W., "Passive Smoking and Lung Cancer," The Lancet II: 595-597, 1983.

In a case-control study in Louisiana (1338 cases, 1393 controls), questions were asked about smoking habits of parents and spouse. Cases were ascertained via hospital admission and pathology records; controls were randomly selected from patients at the same hospital and matched by race, sex and age. For cases, proxy respondents were used for 24%; for controls, there were 11% proxies. Histological confirmation was available for 97% of the cases; bronchioalveolar carcinoma cases were excluded from the study.

For nonsmoking females married to smokers, the following ORs were reported: husband smoked 1-40 pack/years, OR = 1.18 and husband smoked more than 41 pack/years, OR = 3.52. No CIs were given; the second OR estimated was reported to be statistically significant. Regarding parental smoking, the authors wrote, "no significant increases in risk were found in non-smokers."

Confounders were not addressed.

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PASSIVE SMOKING AND LUNG CANCER

PELAYO CORREA LINDA WILLIAMS PICKLE
ELIZABETH FONTHAM YOUPING LIN
WILLIAM HAENSZEL

Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana; Environmental Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; Illinois Cancer Council, Chicago, Illinois, USA

Summary Questions about the smoking habits of parents and spouses were asked in a case-control study involving 1338 lung cancer patients and 1393 comparison subjects in Louisiana, USA. Non-smokers married to heavy smokers had an increased risk of lung cancer, and so did subjects whose mothers smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables indicative of active smoking. It is not clear whether the results reflect a biological effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking. This preliminary finding deserves further investigation.

Introduction

THE possibility of passive or involuntary smoking being a causative factor in lung cancer has been investigated in several countries.[1-3] This report describes a case-control study of lung cancer in Louisiana in which questions were asked about the smoking habits of the spouses and parents of 1338 lung cancer patients and 1393 comparison subjects (controls).

Materials and Methods

Current primary lung cancer cases were identified from admission and pathology records of all participating hospitals in twenty-nine Louisiana parishes (counties), which included all southern, one central (Rapides), and two northern parishes (Caddo and Bossier). Patients with bronchioalveolar carcinomas (32 cases) are not included in the present report. All major hospitals in the study area participated except some in the city of New Orleans where, for logistic reasons, interviewing was deliberately limited to two large hospitals serving the medically uninsured population and two large private hospitals. For each subject a control was randomly selected from patients attending the same hospital and matched by race, sex, and age (within 5 years). Patients whose main diagnosis was emphysema, chronic bronchitis, chronic obstructive pulmonary disease, or cancer of the larynx, oral cavity, oesophagus, or bladder were excluded from the control selection procedures. The admission diagnoses of the controls were distributed in the following categories: cardiovascular 15·3%; gastrointestinal 13%; musculoskeletal 10%; genitourinary 7·3%; ophthalmology and otorhinolaryngology 6·6%; other tumours 5%; diabetes 5%; trauma 3·7%; peripheral vascular 3·7%; pulmonary 2·7%; cerebrovascular 2·5%; and infections 2%.

Local professional interviewers, trained for this investigation and thoroughly familiar with local culture, interviewed subjects (76% of the cases and 89% of the controls) or their next of kin. The questions covered occupation, residency, diet, smoking and drinking habits, health, water supply, and other related items. Information elicited on the smoking habits of the spouse or parent included type of material smoked, duration of smoking habit, and daily amount. Questions on parental habits referred to the period "during most of your childhood". Histological confirmation was obtained for 97% of the cases. Missing data were excluded from the tables. Standard unmatched pair methods were used to estimate relative risks. All p values are based on 2-sided χ^2 tests.

Results

Spouse Smoking

We identified non-smokers with lung cancer and compared the smoking histories of their spouses with those of spouses of non-smoking controls. Only 10 out of 1036 male cases were non-smokers: 2 reported occupational exposure to dust (street-sweeper, log-cutter); 1 was a steam-pipe fitter; 2 lived in the immediate vicinity of industrial plants (grain elevator and cement, oil refinery); 1 was married to a heavy smoker; and 4 were long-time chewers of tobacco. There were 25 non-smoking, ever-married women with lung cancer out of 302 female cases; 2 of these chewed tobacco regularly. For 1 female and 2 male non-smoking patients no information was available on the smoking history of the spouse. 2 female patients' husbands were smokers but the amount and duration was unknown.

Table I distributes the non-smoking, ever-married men and women according to total lifetime pack-years smoked by their spouses at the time of the interview. The relative risk of lung cancer is raised when the spouse is a heavy smoker.

Similar tabulations for smoking subjects did not show an increased risk associated with smoking of spouses, except for light smoking men (less than 20 pack-years), who had a relative risk of 1·5 when married to heavy smokers (41 pack-years or more). Case-control comparisons based on current daily number of cigarettes smoked by the spouse yielded almost identical findings, including relative risk estimates, with those presented in table I. The apparent passive exposure effect was present in women over and under 60 years of age, although small numbers made the subgroup findings not statistically significant. Analyses limited to cases and controls interviewed in person indicated that systematic bias in personal versus next-of-kin responses can be ruled out as a potential explanation for the findings. The same conclusion was reached when relative risks were race adjusted. Inclusion of bronchioalveolar carcinomas resulted in slightly lower odds ratios: males 1·69, females 1·77, both sexes 1·75.

Parents' Smoking Habits

Smoking habits of the parents strongly influenced smoking habits in offspring (table II). Heavy smokers were more likely than the other patients to have had smoking parents. The smoking histories of the parents in our series were associated with each other. There were 201 spouse pairs of smokers, compared with 136 expected if the status of each parent was

TABLE I—NON-SMOKING, EVER-MARRIED LUNG CANCER CASES AND CONTROLS AND LIFETIME CONSUMPTION OF CIGARETTES BY THEIR SPOUSES

	Cigarettes smoked by spouse (pack-years)		
	None	1–40	≥41
Males			
Cases	6	2	0
Controls	154	20	6
Odds ratio	1·0	2·0	
Females			
Cases	8	5	9
Controls	72	38	23
Odds ratio	1·0	0·18	3·52*
		2·07	
Both sexes			
Odds ratio (adjusted for sex)	1·0	1·48	3·11*

*$p<0·05$.

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TABLE II—CIGARETTE USE OF CONTROL SUBJECTS BY SMOKING CATEGORY OF THEIR PARENTS

	Father smoker		Mother smoker	
	Yes	No	Yes	No
Males				
Non-smokers	18%	32%	8%	27%
Ex-smokers	25%	26%	24%	26%
Current smokers	56%	42%	68%	47%
Total number	475	484	79	880
Females				
Non-smokers	37%	66%	29%	56%
Ex-smokers	20%	14%	15%	17%
Current smokers	43%	20%	56%	27%
Total number	130	154	34	250

independently distributed. Classification of the status of one member, particularly the mother, indirectly conveys information on the status of the marital partner.

When the smoking status of each parent is classified separately the relative risks of lung cancer for persons (both sexes, smokers and non-smokers) with a positive paternal and maternal history of smoking are 1·04 and 1·66, respectively (table III). Scrutiny of the data shows that the increased risk associated with maternal smoking is significant in smoking males (odds ratio 1·4) but not significant in smoking females (odds ratio 1·2). No significant increases in risk were found in non-smokers but small numbers preclude adequate analysis (there was only one non-smoking lung cancer patient whose mother was a smoker). To remove the confounding effect of the other parent, we considered each subset of cases and controls for which only one of the parents smoked. The respective relative risks, controlled for spouse-smoking status, for positive paternal and maternal histories of smoking were 0·95 and 1·47, respectively. Thus, smoking status of the mother increases the relative risk of lung cancer, but smoking status of the father does not. The effect of maternal smoking did not seem to be dose related; our questionnaire did not cover this point extensively because we doubted whether children could adequately quantitate their parents' smoking history. The relative risk of lung cancer when both parents smoked was 1·66; there is thus no evidence of an additional contribution to risk from paternal exposure, over and above that contributed by maternal exposure.

Given the enhancing effect of parental smoking on the smoking habits of the offspring, the effect of parental smoking on relative risk of lung cancer could reflect a subtle indirect association with active smoking by the subject. To control for active smoking, a logistic regression analysis was done, taking into account all the active smoking variables which increase lung cancer risk: age at which case started smoking, tar content of usual brand, degree of inhalation, use of hand-rolled cigarettes, years of smoking, maximum amount smoked. By this method of analysis the relative risk associated with maternal smoking was: 1·36 ($p<0·02$) for both sexes and 1·5 ($p<0·01$) for males. No increase in risk was found in this model for female subjects or for subjects whose fathers smoked. The risk was significantly raised only in male smokers whose mothers smoked.

TABLE III—LUNG CANCER CASES AND CONTROLS (BOTH SEXES COMBINED) ACCORDING TO PATERNAL AND MATERNAL SMOKING HISTORY

	Father smoker		Mother smoker	
	Yes	No	Yes	No
Lung cancer	579	590	182	1054
Control	615	652	126	1214
Odds ratio—crude	1·04		1·66†	
Odds ratio adjusted for active smoking (logistic regression—see text)	0·83		1·36*	

*$p<0·05$. †$p<0·01$.

Discussion

Spouse-smoking Effect

Our data strengthen the contention that heavy smoking by one member of the spouse pair increases the lung cancer risk of the non-smoking partner. Heavy smoking by wives may increase the risk of the light smoking husband but this finding requires further analysis and confirmation in larger series. Smoking by husbands did not affect the risk of lung cancer in women who smoked (relative risk 1·03), a finding that suggests that active smoking is so powerful that it overshadows any possible additional effect from concomitant passive exposure.

The proportion of lung carcinomas that were adenocarcinomas in non-smoking women was 54%, compared with 22% for smoking women. The association of adenocarcinoma with smoking is weaker than for other histological types. The risk of squamous and small cell carcinomas among smokers, relative to a unit risk for non-smokers, has been reported to be 15·4, compared with 5·1 for adenocarcinoma.[4] Table I may therefore reflect dilution of the relation by inclusion of adenocarcinomas. Exclusion of adenocarcinomas produced a significant linear trend in risk, as found by Trichopolous et al.[2] The possibility that differences in the chemical composition of mainstream (active) and sidestream (passive) smoke may produce different proportions of histological types of tumours should be considered. The nitrosamine content in sidestream smoke is reported to be approximately 50 times greater than that in mainstream smoke.[5]

The effect of the smoking habits of the spouse on lung cancer risk was first reported by Hirayama in a Japanese cohort study.[1] A cohort study in the United States reported a positive but not significant increase in risk for non-smoking women married to smoking husbands.[3] A case-control study of non-smoking women diagnosed as having lung cancer in Greece reported relative risks of approximately 2·5 for those married to moderate smokers and 3 for those married to heavy smokers, with a significant linear trend.[2] Our numbers are small but we think that the similarity between our findings and those of Trichopolous et al[2] strengthens the suspicion that passive smoking may contribute to lung cancer risk.

Parental Smoking Effect

As far as we know, ours is the first case-control study of lung cancer reporting on parental smoking history. Parents' smoking behaviour influences the smoking habits of their offspring,[6,7] but we found that the smoking behaviour of the father does not influence the lung cancer risk of his offspring, whereas the behaviour of the mother does. This difference may reflect the closer and more prolonged contact that infants and young children have with their mothers than with their fathers.

The risk of bronchitis and pneumonia is increased in children whose mothers smoke.[8,9] This effect is dose related and is greater in the winter, strongly suggesting that passive smoking by the infant is causally related to risk of respiratory infection. The excess of bronchitis occurs after 6 months of age, suggesting that the passive immunity transferred from mother to child prevents bacterial colonisation of bronchial mucosa. The effect of passive smoking on bronchitis may be independent of the mutagenic effect of the tobacco smoke,[10] and it is probably safe to assume that the child is exposed to

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both the irritant and the mutagenic insults carried by sidestream smoke. The observation that the bronchitis attributable to passive smoking occurs mostly during the first year of life and is independent of birth weight may reflect the intimacy of mother-child contact in that period of the child's life.[11] Bronchitis in infants may have a long-lasting effect on the respiratory tract as suggested by the increase in the prevalence of cough at age 20 in subjects who have had a respiratory illness during the first 2 years of life, independent of current smoking habits.[12]

Whether bronchitis is a causative factor in lung cancer is confounded by the fact that smoking induces both cancer and bronchitis. Cohort studies have concluded that "persons who smoke cigarettes run a higher risk of chronic bronchitis than non-smokers and those who develop bronchitis run a higher risk of developing lung cancer".[13]

How maternal smoking causes lung cancer can at this stage only be a matter of speculation. By itself, passive smoking during childhood may not be sufficient stimulus for carcinogenesis. However, laboratory work has shown that: transplacental exposure to carcinogens increases the carcinogenic response to post-natal exposure to the same or to a different carcinogen;[14-15] benzo(a)pyrene, a mutagenic carcinogen found in tobacco smoke, when injected into pregnant mice, induces cancer of the lung and other organs of the offspring;[16] tumours develop in 33% of the offspring of pregnant hamsters treated with high doses of cigarette smoke condensate;[17] and small doses of carcinogens can induce tumours in fetal tissue.[18]

The effects of maternal smoking are only significant in males, especially the heavy smokers. Perhaps maternal smoking enhances active smoking by the offspring in subtle ways not detected by conventional techniques. If our methods for controlling for active smoking are not sufficiently refined, the increase in risk associated with maternal smoking would not be an effect of passive smoking but one of enhancement of active smoking behavioural patterns. This is a real possibility and we would like to encourage further research on the subject.

Conclusion

The differences between the effects of passive exposure to spouse and maternal smoking are puzzling. Passive exposure to spouse smoking is mostly detected in non-smokers and light smoking males; maternal passive smoking effects are seen mostly in smokers. Passive smoking from spouses is introduced in adult life and in smokers is concurrent with their own active smoking. The magnitude of such an effect may be low when compared with active concomitant smoking and it may not be detectable when both types of smoking are present.

Maternal smoking, on the other hand, exerts its influences early in life and in the absence of active smoking is probably insufficient to produce carcinogenic effects. Our findings indicate that maternal smoking results in a slight increase in lung cancer risk but do not indicate whether the effect is due to enhanced active smoking of the offspring or to enhanced susceptibility to lung cancer induction after the challenge of active smoking later in life.

Our findings point to the need for more research on the subject of passive smoking and cancer. Since large numbers of cases may be needed for adequate epidemiological analysis, multi-institutional collaboration may be indicated.

This was supported by contract N01-CP-91023,DCCP, National Cancer Institute, National Institutes of Health (South Louisiana) and by a grant from the Louisiana Chapter of the American Cancer Society (North Louisiana).

Correspondence should be addressed to P. C., Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana LA 70112, USA.

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ANAPHYLACTOID REACTIONS TO NEUROMUSCULAR BLOCKING AGENTS: A COMMONLY UNDIAGNOSED CONDITION?

P. R. YOUNGMAN K. M. TAYLOR
J. D. WILSON

Departments of Medicine and Pharmacology, University of Auckland School of Medicine, Auckland, New Zealand

Summary A group of 28 patients with extreme, life-threatening sensitivity to suxamethonium was identified and 15 were studied in detail by skin-testing. The female/male ratio was 8/1. Sensitivity may be present without previous exposure to suxamethonium; in 3 patients reactions occurred during the first exposure to anaesthesia. Most patients showed one or more cross-sensitivities to alcuronium, tubocurarine, and gallamine. Signs of circulatory collapse were the sole presenting feature in 50% of the patients. Histamine release induced by the drug in vitro was demonstrated in some instances.

Introduction

DRUGS of the muscle-relaxant group are commonly implicated in systemic reactions, sometimes life-threatening, which occur during general anaesthesia. Since 1977 patients at our hospital who have had severe anaesthetic reactions have been skin-tested to determine drug sensitivity. After two deaths attributed to suxamethonium in Auckland in 1982, a study of known sensitive patients was undertaken, initially to determine whether 'Ethycholine', the only suxamethonium chloride available in New Zealand, differed in provoking

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Buffler, P.A., Pickle, L.W., Mason, T.J. and Contant, C., "The Causes of Lung Cancer in Texas," Lung Cancer: Causes and Prevention, eds. M. Mizell and P. Correa (New York: Verlag Chimie International, 1984): 83-99.

This population-based case-comparison interview study examined individuals in six Texas counties "to evaluate the association of lung cancer with occupational and other environmental exposures." Only cases with histological or cytological confirmation were included in the interview phase. A total of 935 cases (460 females, 475 males) and 948 frequency-matched controls were interviewed. In excess of 75% of the interviews in each category were with proxy respondents (next-of-kin).

Adjusted (for personal smoking status) odds ratios for nonsmokers living with a household member who smoked regularly were 0.52 (95% CI 0.15-1.74) for males (based on 5 cases, 56 controls) and 0.78 (95% CI 0.34-1.81) for females (33 cases, 164 controls). The authors reported no statistically significant trend for increased risk with increased years of living with a smoker in females; they noted a suggestion of increasing risk in males, but noted their small sample sizes as well. None of the RRs reported in this part of the analysis was statistically significant.

Statistically significant increased ORs were reported for males employed in construction, chemical, metal and transportation industries, and for females employed in clerical occupations.

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Lung Cancer:

Causes and Prevention

Proceedings of the International Lung Cancer Update Conference, held in New Orleans, Louisiana, March 3-5, 1983

Edited by

Merle Mizell and **Pelayo Correa**

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To

Alton Ochsner, MD

It is fitting that this conference is dedicated to my father, Alton Ochsner, since at one time he stood alone in the belief that smoking was a cause of carcinoma of the lung. It was a stand from which he never swayed, despite the criticism he suffered from his colleagues.

My father fought furiously for that which he believed and yet was willing to change if proved wrong. In looking through his bibliography the other day, I came across an editorial he wrote in 1937 in Surgery, Gynecology & Obstetrics, *entitled "Empiricism in Medicine." In this editorial he stated that Galen's teaching that "pus was laudable" was observed empirically for centuries before doctors realized that pus was not laudable. Because of the adherence to Galen's teaching, many died unnecessarily and others bore pain, suffering, and disfiguration beyond belief. The editorial emphasized to me that my father always taught that one must learn and change with time. He first suggested in 1936 that smoking was a cause of cancer of the lung and championed this hypothesis for years, despite the fact that he was ridiculed by some of his peers: at a particular national meeting when he projected a slide which showed the incidence of carcinoma of the lung and sales of cigarettes having a parallel graph, another surgeon imposed on his slide the sales of brassieres to mock his theory.*

Dr. Evarts Graham, his Professor of Surgery at Washington University and who later became as adamant as my father as an antismoking crusader, told my father, "You are going to crucify yourself if you continue to say there is a relationship between cancer of the lung and smoking. The medical profession will think you are nuts." Many years later when Dr. Graham developed cancer of the lung, he wrote to my father and stated that he wished he had listened to him, for had he done so, he would certainly have lived longer.

Although my father was dogmatic in certain spheres, his mind was flexible enough to change when statistics proved him wrong. He championed pneumonectomy as the treatment for cancer of the lung, feeling that in order to have an adequate cancer operation, one had to remove the entire organ. He felt this so strongly that if he performed a minor resection of a lung tumor which at surgery appeared to be benign and yet on histological examination proved to be malignant, he would return the patient to the operating room and do a radical pneumonectomy. When the statistics of Dr. William Overholt showed that treatment of cancer of the lung was equally as good with lobectomy as with pneumonectomy, Dad was prompt in changing his teaching and accepted lobectomy as the principal means of eradicating cancer of the lung.

People remember this man as a scholar, innovator, teacher, and exceptional civic leader.

John Ochsner, MD, Chairman
Department of Surgery
Ochsner Clinic

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Preface

. The main cause of lung cancer is cigarette smoking; about that the scientific work reported in this book leaves no doubt. Approximately 90% of the deaths from lung cancer and almost one-third of the deaths from cancer of all kinds can be traced directly to smoking. In 1982, about 129,000 Americans died from smoking-related cancers, according to estimates from the Office of Smoking of the U.S. Department of Health and Human Services. But cancer is not the only disease smokers have to fear: the habit also causes elevated rates of heart disease.

According to research reported in this volume, about one in four regular cigarette smokers will be killed before their time by the habit. And the magnitude of the problem is greater than usually is realized. Of every 100 healthy young male smokers in England, statistics predict that one will die a victim of violent crime, two will be killed in traffic accidents, and 25 will die from a disease brought about by cigarettes. Similar proportions of deaths will occur in the United States. Women are quickly gaining equality with men in the lung cancer arena: in 1982, lung cancer surpassed breast cancer as the leading cause of cancer deaths among women in eight states. The pattern, which is believed to be nationwide, is attributed to an increase in smoking which began among women 30 years ago.

The cost for smokers is high in terms of dollars as well as health. In Louisiana, where 2,100 persons die every year from lung cancer, more than $300 million annually are spent on the purchase of cigarettes and medical costs and loss of earnings account for approximately $586 million per year. The state—especially its southern area—has one of the highest cancer rates in the nation, and many of the studies in this volume look at some of the reasons.

Several papers demonstrate that smoking no longer can be considered a personal habit concerning only smokers. Passive smoking—smoke inhaled from nearby smokers—increases the lung cancer rate. Research conducted in Japan has demonstrated that nonsmoking wives of heavy smokers suffer a lung cancer risk at least twice as great as nonsmoking wives of nonsmoking husbands. Research has also shown that radioactive materials are a common component of cigarette smoke. Other studies in the book explore the relationships of nutrition, smoking, and lung cancer: a precursor of vitamin A that comes from green and yellow vegetables can perhaps lower cancer risks. Smoking can work synergistically with occupational exposure to cancer-inducing agents to increase dramatically the risk of lung cancer. Studies have shown that some individuals may have genetic factors that make them more susceptible to certain environmental carcinogens.

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Cigarette smoking is a form of drug dependence because nicotine is an addiction-causing drug. And cigarette smoking is *known* to cause cancer. The addiction to this toxic drug produces many times more deaths than addictions to marijuana, morphine, and cocaine combined. Yet those drugs are illegal. Why then, one may ask, are cigarettes advertised and sold all over the world? When cigarette addiction began about 60 years ago, its deleterious effects on health were not known because smoking-induced cancers can take as long as 30 years to develop. Now, cigarettes are a multibillion dollar industry with extremely well-organized lobbies and advertising efforts. Well over $1 billion each year are spent on efforts to promote this addictive and deadly drug; that sum is more than the total budget of the National Cancer Institute.

What can be done? Some of the research in this volume explores the alternatives. Abolishing smoking, of course, is unrealistic, but other efforts hold promise. Reducing tar in cigarettes may, over the years, reduce cancer rates, but in absolute numbers, lung cancer deaths are likely to go on increasing well into the twenty-first century due to saturation marketing efforts and increases in absolute numbers of smokers. Public education efforts about the deadly effects of smoking are inadequate at the present time and could be made much more effective. And legislation—with higher taxes—can make a difference. In Finland ambitious new laws were enacted in 1977: these laws prohibited advertising and sales promotion of cigarettes; forbade smoking in all public places except in designated areas; outlawed the sale of tobacco products to persons under 16 years of age; reserved money from tobacco tax revenue for developing health-oriented government tobacco policy; and made the government responsible for establishing the limits of harmful components in tobacco products. Finland now leads the world in reducing lung cancer deaths, especially in younger individuals.

The best way to change smoking patterns, which would automatically affect lung cancer occurrence, is to convince young people never to begin smoking. Parents must be aware of their responsibilities as role models and schools should make a health education program emphasizing the hazards of smoking a part of instruction from kindergarten through college.

The college students from Tulane's Chapter of Alpha Epsilon Delta, recognizing the hazards of smoking, helped with various phases of the conference and continue to sponsor antismoking activities. In fact, plans for this book began when Alton Ochsner became an honorary member of AED (the National Pre-Medical Honor Society). We were seated around a banquet table in a New Orleans garden district restaurant when the International Lung Cancer Update Conference was first discussed. Dr. Ochsner planned to present a short history of lung cancer at the conference, for as he told us ". . . . . this disease has grown up with me. It did not exist when I was a medical student." Unfortunately Alton Ochsner died before the conference convened, so this volume lacks his historical perspective. Nevertheless, this book is dedicated to the memory of Alton Ochsner and we were pleased to have his son, John Ochsner, participate in his stead. We gratefully acknowledge the continuing

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aid of the student members of AED and their antismoking efforts; as well as the help of Diana Pinckley, Director of Tulane University Relations, and her efficient staff for their aid in cover design and various aspects of production. The organizers of the conference are especially indebted to Lorraine Mizell, whose untiring work helped make the meeting a success and whose continuing efforts and administrative expertise helped produce this monograph.

The conclusion is clear: cigarette smoking causes lung cancer. If scientists and concerned citizens can communicate that simple message to the public, the cigarette advertising salvos and lobbying efforts may all be for naught. There will then be hope of controlling this disease.

Merle Mizell, PhD
Pelayo Correa, MD

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Acknowledgments

I speak on behalf of Tulane Medical Center when I say that we are pleased and proud that Tulane University has served as one of the cosponsoring universities of this International Lung Cancer Update Conference.

It is fitting that this monograph be dedicated to the memory of Alton Ochsner, MD, an honorary alumnus of Tulane School of Medicine. He served on the Tulane faculty for many years as professor and chairman of surgery, prior to establishing along with four other Tulane department heads what has become the Alton Ochsner Medical Foundation. Dr. Ochsner, an internationally known surgeon, dedicated his life to the elimination of lung cancer.

We have come far in the battle against lung cancer, but there is still much more we can learn about the etiology, prevention, treatment, and ultimately the elimination of lung cancer as a significant cause of human suffering. It is through participation in cooperative efforts such as this international conference that we hope to provide an exchange of information which will lead to even more answers about lung cancer.

John J. Walsh, MD, Chancellor
Tulane University Medical Center

I am glad to acknowledge the success of the joint efforts of our institutions: Louisiana State University, Tulane University, Cancer Association of Greater New Orleans, and the Board of Regents in organizing and carrying out the International Lung Cancer Update Conference.

The conference addressed an issue of great importance to our community and provided up-to-date presentations by some of the best international experts in the field. The conference has already stimulated important discussions in our scientific community and has established an objective scientific basis to approach the lung cancer problem in our state. I hope the impetus provided by the conference will continue until a strategy for prevention is developed.

Paul F. Larson, MD, Dean
Louisiana State University
School of Medicine in New Orleans

The Louisiana Board of Regents and its Advisory Committee on Research and Development are pleased to have had the opportunity to sponsor the International Lung Cancer Update Conference. The state of Louisiana, its citizens, and its institutions of higher learning are all beneficiaries of this meeting.

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As a result of bringing the world's authorities on lung cancer research together in New Orleans to present and exchange research findings about the state of the art in this field, the world has seen that Louisiana is seriously concerned about this dread disease and intends to promote scientific research in order to address this problem. Therefore the state's image with the scientific community has been enhanced worldwide.

Louisiana's citizens have benefited from this conference because they received the most current and reputable advice from the foremost experts in the field about what they can do to enhance their chances of living lung-cancer-free lives. They learned that this disease is largely self-inflicted.

Finally the scholars, scientists, and medical practitioners in Louisiana's institutions of higher learning, as well as the scientific community outside our colleges and universities, have benefited from the opportunity to exchange information with, ask questions of, and interact with the experts who participated in this conference.

The International Lung Cancer Update Conference was a tremendous success, and we at the Board of Regents are extremely pleased to have been a part of it.

William Arceneaux, PhD
Commissioner of Higher Education
Louisiana Board of Regents

Sponsoring a conference is an uncommon event for the Louisiana Board of Regents' Research and Development Program. Generally only research projects which address issues that are of particular concern to the state (eg, hazardous waste, economic development, wetlands, the state's high incidence of cancer) are supported with these state-appropriated funds. Since one of the goals of this program, however, is to upgrade the quality of research in Louisiana's institutions of higher learning, the Board of Regents and its Advisory Committee on Research and Development decided that sponsorship of this conference not only was appropriate, but also would be a decided investment in the future of quality cancer research in the state.

In sponsoring this conference, the state provided its scientists a rare and perhaps unique opportunity to learn from and exchange ideas with the world's foremost authorities in the lung cancer field in a convenient location and forum. The knowledge and information the state's scientists gleaned as a result of this conference should stimulate interest in this area, as well as promote the submission of research applications to the R&D Program that are at the forefront of knowledge in this field.

The response to this conference from the Louisiana scientific and medical communities was overwhelmingly positive. The Board of Regents was fortunate that the organizers of the conference were responsible and talented individuals who undertook this task in a serious and dedicated manner. Their hard work and combined talents, in conjunction with the outstanding speakers and excellent scientific presentations, made the conference an unequivocal success. On behalf

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of the Board of Regents and its Advisory Committee on Research and Development, we thank these individuals for their contributions not only to the R&D Program but also to the continued advancement of knowledge in this state.

Priscilla Kilcrease, PhD, Director
Research and Development Program
Louisiana Board of Regents

The Board of Directors and staff of the Cancer Association of Louisiana, Inc, and the Cancer Association of Greater New Orleans, Inc, a United Way agency, are very proud to have been involved in the planning and coordination of the International Lung Cancer Update Conference held March 3-5, 1983.

Many of the papers presented in the monograph reviewed the smoking habits and the epidemiologic trends in lung cancer incidence and mortality in the United States, Europe, and Japan. They all repeatedly emphasized the importance of cigarette smoking as the major causative factor in lung cancer.

Environmental hazards (eg, air pollution and asbestos) and host factors (eg, genetics and nutrition) play a small role in the overall etiology of lung cancer. The most important conclusion of the International Lung Cancer Update Conference is that an international emphasis should be placed on smoking cessation programs aimed not only at high-risk adult populations but more importantly at all adolescents.

The only rational approach is to prevent lung cancer by getting individuals to either stop smoking or never to start to smoke cigarettes.

Robert G. Weilbaecher, MD, President
Cancer Association of Greater New Orleans, Inc
Cancer Association of Louisiana, Inc

With the high incidence of lung cancer in Louisiana, it was very appropriate for New Orleans to be selected as the host city for the International Lung Cancer Update Conference. The Cancer Association of Louisiana and the Cancer Association of Greater New Orleans are glad to cosponsor a conference that brings together some of the world's lung cancer experts.

Personally, I have appreciated the opportunity to be involved in a program that could help resolve some of the health problems of Louisiana's citizens.

Ruth A. Sherwood, Executive Director
Cancer Association of Greater New Orleans, Inc
Cancer Association of Louisiana, Inc

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CHAPTER 7

The Causes of Lung Cancer In Texas

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PATRICIA A. BUFFLER,* LINDA WILLIAMS PICKLE,**
THOMAS J. MASON,** and CHARLES CONTANT**

* Epidemiology Research Unit, The University of Texas Health Science Center at Houston, School of Public Health, Houston, Texas 77025
** Environmental Epidemiology Branch, National Cancer Institute, Landow 3C15, Bethesda, Maryland 20205

ABSTRACT

A population-based case-comparison interview study of lung cancer was conducted from 1979 to 1982 in six Texas coastal counties—Orange, Jefferson, Chambers, Harris, Galveston, and Brazoria—to evaluate the association of lung cancer with occupational and other environmental exposures. Lung cancer mortality rates in these counties consistently have exceeded lung cancer mortality rates observed for Texas and the United States from 1950–1969 to 1970–1975 for both sexes and races (white and nonwhites).

Histologically and cytologically confirmed incident cases diagnosed during the interval July 1976 to June 1980 among white male and female residents aged 30–79 years were ascertained from participating hospitals in the six-county area. Both population-based and decedent comparisons were selected and matched on age, race, sex, region of residence, and vital status at time of ascertainment.

The exposures of primary interest in the study of lung cancer are those associated with occupation (employment in specific industries and occupations) in conjunction with tobacco, alcohol, diet, and residential exposures.

Key Words: Smoking history, petrochemical industry, histologic types, construction workers, chemical manufacturing, transportation

Introduction and Background

Data presented by Doll and Peto (1) and related reports (2) indicate that respiratory cancer sites, dominated by lung cancer, show the most dramatic increases of all cancer sites over the past 30 years. The role of smoking in the etiology of respiratory cancer has been well documented. In addition, lung cancer is

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Lung Cancer Causes and Prevention

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recognized as possibly the most important work-related cancer. However, the interaction between smoking and occupational exposures and the increased risk that may be attributed to an occupational exposure has not been very well characterized for a large number of workplace exposures.

A population-based case-comparison interview study of lung cancer, obtaining detailed occupational histories, was conducted in six Texas coastal counties where lung cancer mortality rates were elevated (3). Figure 1 shows the location of the counties of Orange, Jefferson, Chambers, Brazoria, Galveston, and Harris, a highly industrialized area where Houston is located. Approximately 25% (3.5 million) of the total state population in 1980 resided in this southeastern coastal area, the majority (77.5%) in Harris County.

Newly diagnosed, histologically confirmed cases of lung cancer in white females (including Hispanic) were ascertained from July 1977 through June 1980 in Harris County (3 years) and from July 1976 through June 1980 for the surrounding five counties. Similarly, cases among white males (including Hispanic) were ascertained for four years (July 1976 through June 1980) for the five less urban but industrialized counties, excluding Harris County. Background lung cancer mortality rates for white males and females were examined by Texas State Economic Area

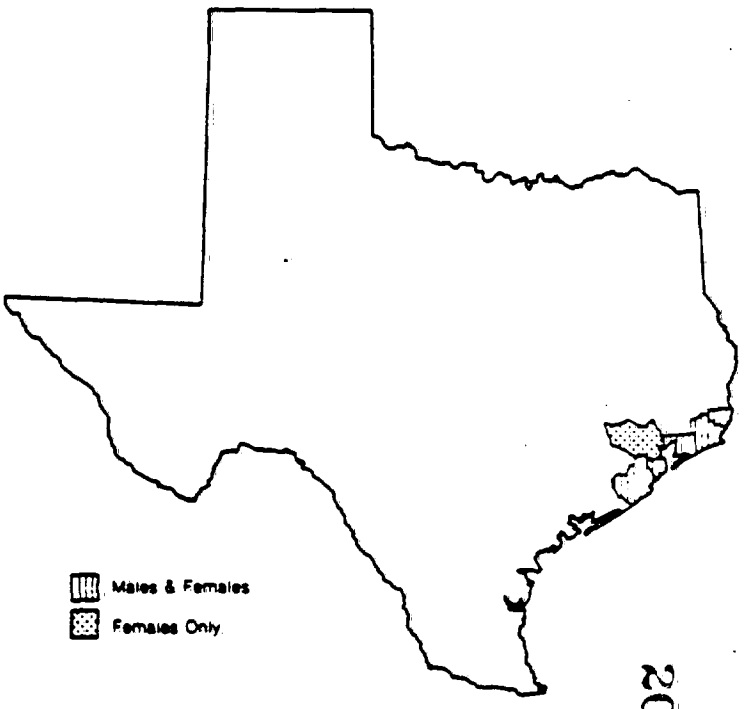

Figure 1. Texas lung cancer study area.

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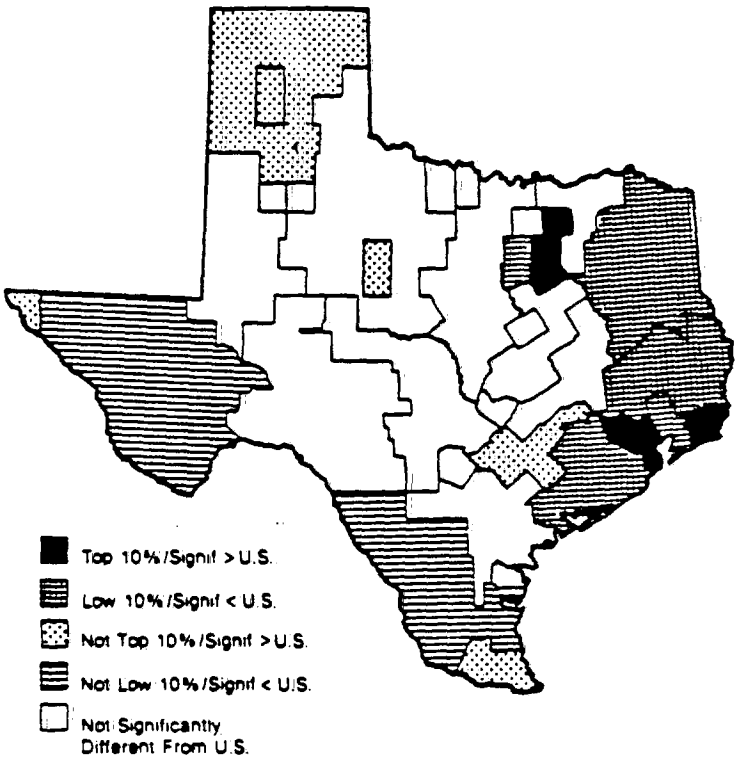

Figure 2. Lung cancer mortality 1970–1975 for white males.

(SEA) for the time period (1970 to 1975[1]) immediately preceeding the case-comparison study. As shown in Figures 2 and 3, these maps consistently document the significantly higher lung cancer mortality rates observed earlier for both white males and white females in these Texas coastal counties. The dark areas along the upper Texas coast are the Beaumont SEA (Orange and Jefferson counties), the Houston SEA (Harris County), and the Galveston SEA (Galveston County). Age-adjusted mortality rates (adjusted to the 1960 United States population) in these areas are in the top 10% of rates for SEAs in the United States and are significantly higher than the white male or white female lung cancer mortality rate for the total United States population. For white females in Harris County, this excess was notable for both the rate and the trend in the rate from 1950 to 1975 (4). For all ages, combined, the overall excess in lung cancer mortality in the Texas study area is approximately 30–40%, but this is considerably greater for some age groups.

Occupational and industrial exposures of importance for residents of the Texas coastal area include those associated with shipbuilding and repair, chemical and

[1]Excluding deaths for 1972.

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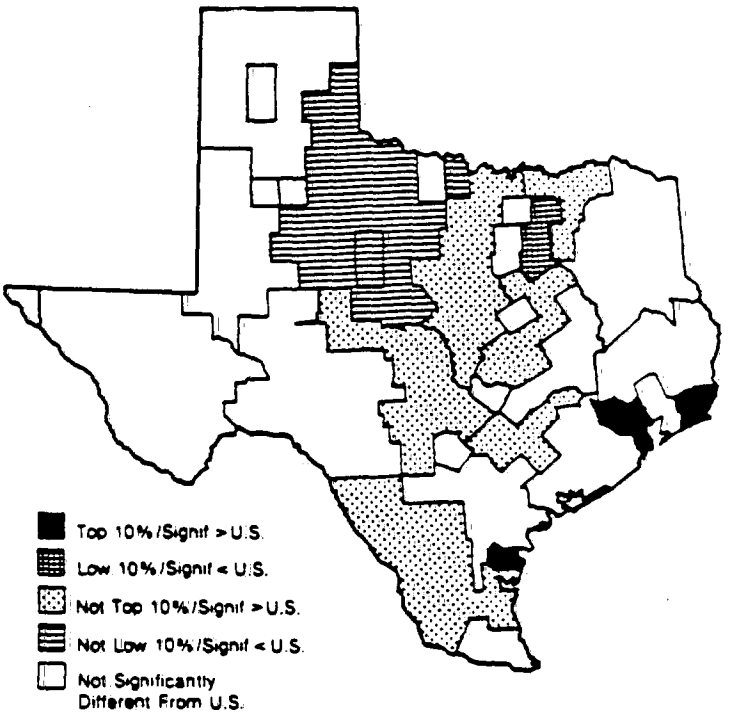

Figure 3. Lung cancer mortality 1970–1975 for white females.

petrochemical manufacturing, petroleum refining, construction, and metal industries. The largest United States based chemical and synthetic rubber production facilities are located in the study area, so a high proportion of the working population currently is employed or has been employed in these industries. For some of the smaller counties, such as Orange and Jefferson, where a single industry is dominant, as high as 27% of the working population reported being currently employed in chemical and allied products manufacturing compared with 2% for Harris County (5).

Methods

Histologically confirmed incident cases of lung cancer diagnosed among white male and female residents (including Hispanic) of the study counties for the designated time intervals (July 1977 through June 1980 for females in Harris County and July 1976 through June 1980 for males and females in other counties) were ascertained by review of hospital and state records. Hospitals in the study area that were not already participating in the Statewide Cancer Reporting Program

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were contacted and asked to participate in the study. Population-based and decedent comparison subjects were selected from state and federal records and matched to cases on age, race, sex, vital status at time of ascertainment, and county of residence (Harris County or other five counties). Hispanic study subjects were identified systematically by use of an algorithm to identify Spanish surname. Medical records were abstracted by state-trained abstractors to obtain relevant disease and demographic data. Following contact with the family physician (for cases only), personal interviews were conducted with study subjects or with the next of kin of decedent cases and comparison subjects, using established criteria for selecting the most appropriate next of kin respondents. Interviews were conducted by trained interviewers in the home using a standardized interview protocol. Detailed information regarding the primary exposures of interest was collected, specifically smoking history, work history, residential history, and drinking history.

Industries of employment were coded to the Standard Industrial Classification (SIC) (6) and occupations were coded using the *Dictionary of Occupational Titles* (7). The Mantel-Haenszel summary chi-square and odds ratio statistics were calculated (8). Confidence intervals (95%) were calculated using the method of Miettinem (9).

Results

A total of 56 of the 67 hospitals in the six-county Texas study participated in the study, including all of the seven large hospitals (500 or more beds). Ten of the 11 smaller hospitals that did not participate were located in Harris County. Therefore we were able to ascertain 92.2% (1520 cases) of the total 1649 incident white male and female lung cancer cases (including Hispanic) estimated for the 3- to 4-year interval (mid-1976 or 1977 to mid-1980). The number of incident cases was estimated by adjusting age–race–sex–county mortality rates by population growth and an incidence: mortality ratio of 1.35:1.0. Case ascertainment was higher for residents of counties other than Harris County, 97.2% vs 82.1% (Table 1). A total of 766 female and 754 male cases were ascertained representing, respectively, 88.7 and 96.1% of the total estimated incident cases ascertained. Hispanic females appear to be poorly ascertained (38.1%), but this may be related to the classification based on Spanish surname which may not be an effective technique for ascertaining married Hispanic females.

All ascertained cases will be used for determining age–race–sex and county lung cancer incidence rates for the study area. A total of 88.9% of the ascertained cases were included in the interview study. Some cases (110, or 7.2%) lacked histologic or cytologic confirmation of lung cancer and were ineligible for the case-comparison study. For the majority of these cases (79, or 71.8%) the basis of the lung cancer diagnosis was radiologic or clinical evidence. There was insufficient diagnostic information available on the remaining 31 cases. Additional losses of study subjects in the case-comparison study were related to race and residential eligibility criteria; unable to locate; moved out of interview area; physician,

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Table 1. Lung cancer case ascertainment in Texas study by sex, ethnic group, and area, 1976–1980

	Number estimated	Number ascertained[a] (%)	Number cases interviewed[b]
White Females			
Anglo	822	750 (91.2)	449
Spanish surname	42	16 (38.1)	11
Total	864	766 (88.7)	460
White Males			
Anglo	767	730 (95.2)	460
Spanish surname	18	24 (133.3)	15
Total	785	754 (96.1)	475
Area			
Harris County (females only, 1977–1980)	567	468 (82.1)	275
Other counties	1082	1052 (97.2)	660
Total	1649	1520 (92.2)	935

[a] Includes 110 cases without histologic confirmation and an additional 15 cases estimated to be ineligible, in terms of race and residence criteria.

[b] Excludes cases ineligible, not located, refusals by physician, hospital or study subject, and cases interviewed and subsequently identified as ineligible, or data to be of poor quality.

Table 2. Texas lung cancer study population by sex, study group, and ethnicity

	Study group		
	Cases	Controls	Totals
Total			
Female	460	482	942
Male	475	466	941
Total	935	948	1883
Spanish surname			
Female	11	20	31
Male	15	19	34
Total	26	39	65

hospital, and subject refusals; and poor quality interview data. Overall study subject refusal rates were 7.7% and 10.7% for decedent cases and controls respectively, and 13.5% and 20.6% for living cases and controls, respectively. A total of 935 interviews was completed with eligible cases (460 females and 475 males) and 948 interviews with frequency matched comparison subjects (Table 2). Included in these totals are 26 Spanish surname cases and 39 comparison subjects. Separate analyses are not presented at this time for these study subjects.

The average duration of time study subjects resided in the county of diagnosis or in the six-county study area is over 25 years for all study groups. The majority of both male (86%) and female (82%) cases were decedent cases and were slightly older at time of diagnosis than the living cases (Tables 3 and 4). The distribution of age at diagnosis is compared for male and female study groups in Figure 4. A higher proportion of the female cases was diagnosed before age 60 (45.4%) than male cases diagnosed before age 60 (34%).

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 3. Number and percentage of male lung cancer cases by age at diagnosis and type of respondent, Texas, 1976 to 1980

Age at diagnosis (years)	Type of respondent: Self — Cases No	Cases %	Controls No	Controls %	Next of kin — Cases No	Cases %	Controls No	Controls %	Total — Cases No	Cases %	Controls No	Controls %
30–39	1	1.5	1	1.6	3	0.7	2	0.5	4	0.8	3	0.6
40–49	5	7.5	7	10.9	28	6.9	34	8.5	33	7.0	41	8.8
50–59	23	34.3	22	34.4	102	25.0	98	24.4	125	26.2	120	25.7
60–69	31	47.0	23	35.9	165	40.4	164	40.8	196	41.3	18.7	40.2
70–79 +	7	10.6	11	17.2	110	27.0	104	25.9	117	24.7	11.5	24.7
		100.0		100.0		100.0		100.0		100.0		100.0
Totals	67		64		408		402		475		466	

Table 4. Number and percentage of female lung cancer cases by age at diagnosis and type of respondent, Texas, 1976 to 1980

Age at diagnosis (years)	Type of respondent: Self — Cases No	Cases %	Controls No	Controls %	Next of kin — Cases No	Cases %	Controls No	Controls %	Total — Cases No	Cases %	Controls No	Controls %
30–39	0	0.0	3	2.6	6	1.6	5	1.4	6	1.3	8	1.7
40–49	9	11.1	12	10.3	40	10.6	50	13.7	49	10.6	62	12.9
50–59	36	44.4	55	47.4	118	31.1	104	28.4	154	33.5	159	33.0
60–69	24	29.6	34	29.3	153	40.4	135	36.9	177	38.5	169	35.1
70–79 +	12	14.8	12	10.3	62	16.4	72	19.7	74	16.1	84	17.4
		100.0		100.0		100.0		100.0		100.0		100.0
Totals	81		116		379		366		460		482	

Proportions of male and female cases and comparison subjects using tobacco, cigarettes, alcohol, or who "ever lived with household member who smoked regularly" are compared in Table 5. Ninety-seven percent of the male cases and 91% of the female cases reported ever smoking cigarettes but a higher proportion of the female than male cases reported smoking cigarettes currently, 68% vs 54%. Proportions of heavy smokers and use of alcohol (ever) were higher for cases than comparison subjects and for males than females. An extremely high proportion of both female cases and comparison subjects report having lived with a household member who smoked regularly, 93% vs 88%.

Although the patterns of risk differed for males and females (Table 6), the odds ratios for all smoking variables were statistically significant at the $p = .05$ level. Among males, ex-smokers had a risk higher than current smokers, whereas in females the risk was lower in ex-smokers. The highest odds ratio for females was observed for current smokers, 7.9 vs 5.0 for ex-smokers. Odds ratios for the ac-

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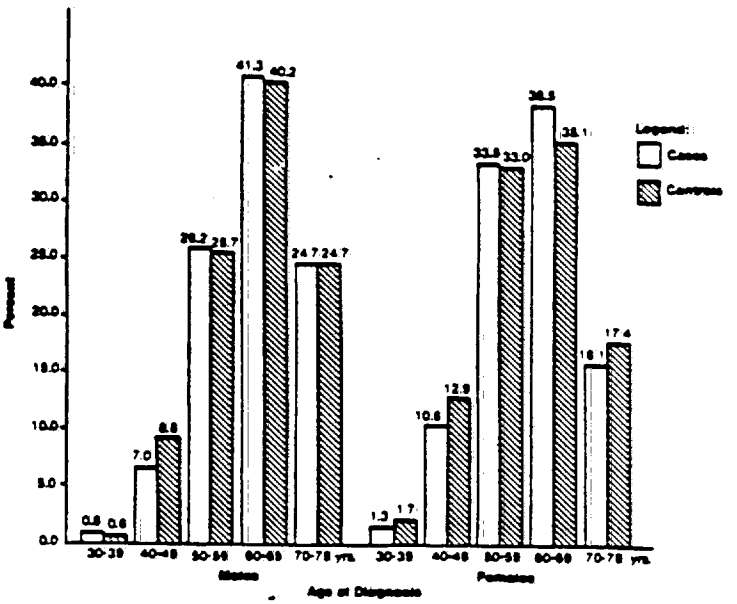

Figure 4. Age distribution (age at diagnosis) for male and female study subjects, Texas lung cancer study, 1976–1980. Clear columns, cases; shaded columns, controls.

cumulated lifetime cigarette dose, expressed as pack-years, were higher for males in the low and moderate categories but associated with a similar gradient in both males and females. No difference in risk was associated with the use of filtered cigarettes for either males or females.

The role of "passive smoking" in contributing to risk of lung cancer was examined (Table 7). In this analysis the crude (or unadjusted) odds ratio are increased and significant for both males and females, 1.4 and 2.1, respectively. However, when the confounding effect of individual subject smoking was controlled by stratifying the

Table 5. Proportion of cases and controls reporting use of tobacco, cigarettes and alcohol by sex, Texas lung cancer study, 1976–1980

	Males		Females	
	Cases	Controls	Cases	Controls
Tobacco (ever)	0.99	0.90	0.91	0.59
Cigarettes (ever)	0.97	0.80	0.91	0.59
Cigarettes (current)	0.54	0.47	0.68	0.38
Cigarettes (light)	0.08	0.10	0.08	0.17
Cigarettes (heavy)	0.45	0.29	0.34	0.13
Alcohol (ever)	0.86	0.81	0.78	0.63
Lived with a smoker	0.76	0.70	0.93	0.88

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 6. Odds ratios* associated with smoking variables for males and females, Texas lung cancer study, 1976–1980

	Males	Females
Ever smoked	10.12	6.89
Current smoker	9.59	7.89
Ex-smoker	10.85	5.00
Pack-years		
Low (0–35)	6.24	3.21
Moderate (36–63)	9.39	7.98
High (64 +)	13.05	13.35
Filtered cigarettes		
Yes	9.39	7.11
No	10.25	6.06
Both	12.27	7.09

*All odds ratios significant at $p < .05$

male and female study groups into smokers (ever) and nonsmokers (never) and examining the adjusted odds ratios, there was no significant increase in risk associated with passive smoking. In fact, the odds ratios for nonsmokers living with a regular smoker were not increased for either males or females, 0.52 and 0.78, respectively. However, odds ratios for smokers living with a regular smoker were increased, although not significantly, 1.28 and 1.80 for males and females. The overall odds ratios (adjusted) associated with passive smoking were only slightly increased and not significant for either males or females, 1.2 and 1.3, respectively. When the possibility of a "passive smoking" effect was examined among nonsmokers by number of years lived with a regular smoker, there was very little difference in risk for females who lived with a regular smoker for 0-32 years (Table 8). The odds ratios for males suggest an increase by are based on smaller numbers than the analysis in females.

Table 7. Odds ratios for passive smoking (household member smoked regularly) in Texas male and female lung cancer studies, 1976–1980

	Yes		No		Odds ratio	95% Confidence interval	χ^2
	Case	Control	Case	Control			
Males							
Crude	363	329	93	119	1.41*	1.04, 1.92	4.8
Self ever smoked							
No	5	56	6	34	0.52	0.15, 1.74	1.2
Yes	357	273	87	85	1.28	0.91, 1.79	2.0
Overall (MOR)					1.20	0.87, 1.65	1.18
Females							
Crude	429	425	24	51	2.12*	1.29, 3.50	9.05
Self ever smoked							
No	33	164	8	32	0.78	0.34, 1.81	0.3
Yes	396	260	16	19	1.80	0.92, 3.58	3.0
Overall (MOR)					1.30	0.78, 2.18	1.0

*$p < .05$.

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 8. Odds ratios associated with passive smoking

Ever live with household member who smoked	Number	Odds ratio	Confidence interval	χ^2
Males				
Total nonsmokers	61	0.52	0.15, 1.74	1.2
0–32 years	49	0.40	0.10, 1.58	1.8
33+ years	10	1.56	0.30, 8.05	0.3
Females				
Total nonsmokers	201	0.78	0.34, 1.81	0.3
0–32 years	97	0.62	0.24, 1.63	0.9
33+ years	99	0.93	0.38, 2.28	0.0

Histologic types of lung cancer were classified according to the World Health Organization (WHO) classification (10). The four major cell types account for 75–85% of the cases in both the male and female series and the cell type distribution by age group is shown for males and females in Table 9. Adenocarcinoma is the predominant lung cancer cell type in both young (30–49 years) males and females, comprising 37.8% (males) and 38.9% (females) of all lung cancers among persons aged 30–49 years at diagnosis. There is a marked shift with age in this pattern such that for both males and females aged 70 or older at diagnosis the predominant cell type is squamous or epidermoid (accounting for 40.5% of all cases among males and 31.0% among females). Overall, squamous was the predominant cell type among males (42.2%) and adenocarcinoma among females (35.5%). These patterns held for both smokers and nonsmokers except for nonsmoking males, in whom 6 of 11 (54.5%) cases were adenocarcinoma.

The risk associated with smoking was examined by cell type, specifically odds ratios for smoking categories within the adenocarcinoma series compared with nonadenocarcinoma cases (Tables 10 and 11). The odds ratios for smoking categories based on pack-years were all significant, emphasizing the increased risk of lung cancer (all types) associated with smoking. However, the gradient of risk, in both males and females, was markedly different for adenocarcinoma compared with nonadenocarcinoma (all other lung cancer) cell types. There were 104 cases of

Table 9. Male and female lung cancer cases by histologic type and age, Texas, 1976–1980

	Males						Females					
	30–49 years		50–69 years		70+ years		30–49 years		50–69 years		70+ years	
Cell type	No	%	No	%	No	%	No	%	No	%	No	%
Squamous	8	21.6	112	34.8	47	40.5	11	20.4	74	22.6	22	31.0
Small cell	4	10.8	64	20.1	16	13.8	10	18.5	92	28.1	11	15.5
Adenocarcinoma	14	37.8	73	22.9	17	14.7	21	38.9	99	30.3	19	26.8
Large cell	2	5.4	19	6.0	9	7.8	4	7.4	11	3.4	3	4.2
Other		24.4		16.2		23.2		14.8		15.7		12.5
Total		100.0		100.0		100.0		100.0		100.0		100.0

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 10. Odds ratios associated with smoking for lung cancer cell types in males, Texas lung cancer study, 1976–1980

Cell type	Smoking category (pack-years)	Odds ratio	Confidence intervals	χ^2
Adenocarcinoma	Low	3.85	1.44, 10.31	8.04
	Moderate	4.45	1.72, 11.48	10.93
	High	5.38	2.14, 13.56	15.21
Nonadenocarcinoma	Low	6.60	2.75, 15.84	21.57
	Moderate	11.30	4.87, 26.19	43.75
	High	15.41	6.73, 35.25	63.34

Table 11. Odds ratios associated with smoking for lung cancer cell types in females, Texas lung cancer study, 1976–1980

Cell type	Smoking category (pack-years)	Odds ratio	Confidence intervals	χ^2
Adenocarcinoma	Low	2.16	1.18, 3.98	6.37
	Moderate	4.32	2.40, 7.79	26.11
	High	7.80	4.28, 14.20	52.93
Nonadenocarcinoma	Low	4.17	2.34, 7.43	25.80
	Moderate	10.97	6.27, 19.20	86.87
	High	18.90	10.61, 33.67	128.13

adenocarcinoma in the male series and 139 in the female series. A much steeper increase in risk associated with lifetime cigarette dose (pack-years) is observed for all other lung cancer cell types compared to adenocarcinoma. These patterns are summarized in Figure 5.

Preliminary analyses of the detailed work histories is based on the usual occupation and usual industry of employment as reported or as summarized from the work history for self and spouse. Examination of the work histories indicates that approximately 78% of the study subjects spent more than half of their reported working time employed in the occupation reported as their usual occupation. Usual industry of employment was determined by selecting the industry in which a subject was reported to have been employed for the longest duration of time. Odds ratios, adjusted for smoking (ever/never) were determined to identify whether an increased risk was associated with employment in a given occupation or industry for both males and females. Using the Professional/Technical category as a referent for males (odds ratio = 1), none of the odds ratios for the other occupational categories was significantly increased (Table 12). Odds ratios (OR) for usual industry of employment were similarly calculated using the sales category (SIC 50–59) as the referent (OR = 1.0) (Table 13). Significantly elevated odds ratios were observed for several industrial categories, specifically construction (SIC 15–17), chemical manufacturing (SIC 28), metal manufacturing (SIC 33–34), and transportation (SIC 40–49). In addition, an elevated odds ratio (OR = 2.44) of borderline statistical significance (at the .05 level) is observed for oil and gas extraction (SIC 13).

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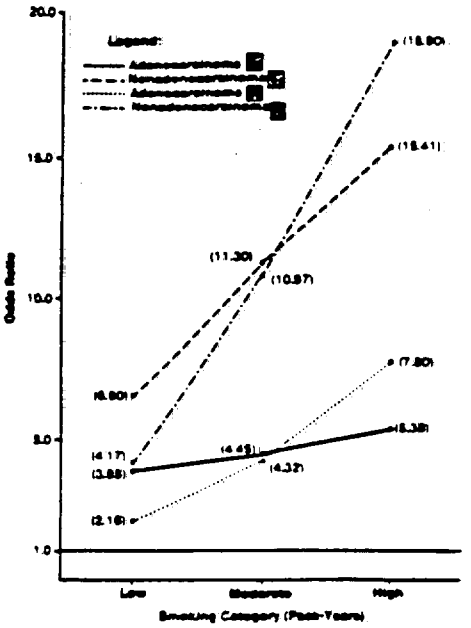

Figure 5. Odds ratios associated with smoking by lung cancer cell type.

The majority (approximately 60%) of the females reported their usual occupation as housewife. Using this category as the referent (OR = 1.0), smoking-adjusted odds ratios (ever/never) were calculated for the remaining categories (Table 14). Although there are several categories with elevated odds ratios, only the odds ratio for the clerical category (1.57) is significant. The odds ratio for the service category (1.57) is similarly increased, and of borderline statistical significance.

Table 12. Adjusted[a] odds ratios for usual occupation in Texas male lung cancer study, 1976–1980

Occupation category	Total number in category (cases and controls)	Odds ratio	Confidence interval	χ^2
Clerical/Sales	94	0.61	0.36, 1.04	3.33
Service	50	1.12	0.60, 2.09	0.13
Agriculture	39	0.89	0.44, 1.84	0.09
Processing	77	0.80	0.47, 1.38	0.63
Machine trades	77	1.37	0.78, 2.39	1.19
Bench work	14	1.04	0.34, 3.19	0.0.
Structural work	275	1.46	0.96, 2.20	3.15
Miscellaneous	140	0.89	0.55, 1.44	0.22
Professional/Technical	157	1.00	— —	—

[a]Adjusted for smoking (ever/never).

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 13. Adjusted[a] odds ratios for usual industry of employment in Texas male lung cancer study, 1976–1980

Industry category (SIC number)	Total number in category	Odds ratio	Confidence interval	χ^2
Agriculture (01–09)	30	1.64	0.70, 3.83	1.31
Oil/gas extract (13)	28	2.44	1.00, 5.97	3.82
Other mining (10–12, 14)	8	0.72	0.19, 2.80	0.22
Construction (15–17)	150	2.56[b]	1.49, 4.41	11.50
Chemical (28)	60	2.16[b]	1.10, 4.24	5.04
Petroleum (29)	178	1.54	0.91, 2.60	2.63
Metals (33–34)	25	3.38[b]	1.36, 8.39	6.90
Shipbuilding (373)	27	1.91	0.83, 4.42	2.29
Other manufacturing (20–39 minus above)	52	1.55	0.77, 3.12	1.51
Transportation (40–49)	120	2.57[b]	1.47, 4.52	10.88
Personal services (60–69, 80, 91–97)	65	1.73	0.91, 3.29	2.76
Professional/Governmental (70–79, 81–87)	85	1.34	0.73, 2.44	0.91
Sales (50–59)	97	1.00	— —	—

[a] Adjusted for smoking (ever/never).
[b] $p < .05$

Table 14. Adjusted[a] odds ratios for usual occupation in Texas female lung cancer study, 1976–1980

Occupation category	Total number in category	Odds ratio	Confidence interval	χ^2
Clerical	161	1.57[b]	1.07, 2.31	5.27
Service	88	1.57	0.96, 2.57	3.22
Agriculture	3	0.74	0.14, 3.92	0.12
Processing	2	4.22	0.43, 41.33	1.53
Machine trades	2	2.66	0.45, 15.93	1.15
Bench work	11	1.67	0.47, 5.97	0.62
Structural	2	5.22	0.79, 34.59	2.93
Miscellaneous	8	2.27	0.52, 9.98	1.18
Professional/Technical	110	1.15	0.75, 1.76	0.40
Housewife	551	1.00	— —	—

[a] Adjusted for smoking (ever/never).
[b] $p < .05$

There were too few observations in the remaining categories for a meaningful analysis. A similar analysis of usual industry of employment for females indicated no categories of concern except for the possible exception of the increase noted for the category of other manufacturing (Table 15).

Smoking-adjusted odds ratios were also examined for the usual occupation and industry of employment for the spouses of both males and females. The only significantly increased odds ratio observed was for the usual industry of employment for spouses of female lung cancer cases. The Construction industry, with 146 cases and controls reporting this as the usual industry for their spouse, was associated with an increased odds ratio of 1.74 (1.04, 2.92; $\chi^2 = 4.40$).

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

Table 15. Adjusted[a] odds ratios for usual industry of employment in Texas female lung cancer study, 1976–1980

Industry category	Total number in category	Odds ratio	Confidence interval	χ^2
Agriculture	6	0.91	0.24, 3.53	0.02
Oil/gas extract	4	2.01	0.37, 10.84	0.66
Other mining	0	—	— —	—
Construction	2	4.95	0.75, 32.69	2.76
Chemical	2	3.93	0.40, 39.06	1.37
Petroleum	6	0.43	0.91, 2.00	1.16
Metals	2	3.93	0.40, 39.06	1.37
Shipbuilding	2	3.93	0.40, 39.06	1.37
Other manufacturing	23	2.70	0.95, 7.67	3.50
Transportation	12	0.78	0.22, 2.76	0.15
Services	74	1.26	0.75, 2.13	0.75
Professional/Governmental	93	1.08	0.69, 1.69	0.12
Sales	113	1.23	0.80, 1.90	0.92
Housewife	592	1.00	— —	—

[a]Adjusted for smoking (ever/never).

Table 16. Odds ratios for household member regularly employed in specific industry for Texas lung cancer study, 1976–1980: Males

Industry	Yes		Odds ratio	95% Confidence interval	χ^2
	Case	Control			
Asbestos manufacturing	6	2	2.60	0.60, 11.25	1.76
Cement manufacturing	5	5	0.99	0.30, 3.25	0.00
Insulation manufacturing	4	1	2.99	0.47, 19.04	1.48
Coal mining	11	4	2.57	0.86, 7.71	3.06
Shipyard/shipbuilding	58	52	1.11	0.75, 1.65	2.27
Demolition	5	3	1.54	0.40, 5.93	0.41
High-rise construction	11	9	1.19	0.50, 2.84	0.16

Table 17. Odds ratios for household member regularly employed in specific industry for Texas lung cancer study, 1976–1980: Females

Industry	Yes		Odds ratio	95% Confidence interval	χ^2
	Case	Control			
Asbestos manufacturing	5	10	0.55	0.20, 1.50	1.29
Cement manufacturing	20	18	1.17	0.02, 2.23	0.24
Insulation manufacturing	9	4	2.24	0.73, 6.94	2.07
Coal mining	7	12	0.63	0.25, 1.57	1.00
Shipyard/shipbuilding	99	102	1.02	0.75, 1.39	0.02
Demolition	5	7	0.77	0.25, 2.33	0.02
High-rise construction	37	26	1.52	0.91, 2.55	2.60

In addition to these analyses specific questions were asked regarding whether anyone in the household ever worked in the following industries: asbestos, cement, or insulation manufacturing; coal mining; shipyards and shipbuilding; demolition;

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high-rise construction. For both males and females a large number of cases and controls reported having a household member employed in a shipyard or in shipbuilding, but this was not associated with an increased odds ratio (1.11 for males and 1.02 for females) (Tables 16 and 17). Among males there were no statistically significant increases; however, the odds ratios for asbestos manufacturing, insulation manufacturing, and coal mining are increased. Similarly, for females the odds ratio is increased for insulation manufacturing and high-rise construction but not significantly.

Discussion

The availability of fairly large numbers of male and female incident lung cancer cases and comparison subjects in an interview study with detailed occupational histories provides an important basis for examining the contribution of occupational exposures to lung cancer in males and females. Recognizing the strong increase in lung cancer risk associated with cigarette smoking, such analyses need to control for smoking differences. Our preliminary analysis of usual occupation and industry of employment with a broad smoking adjustment (ever/never) indicates several occupational and industrial associations that need to be pursued in future analyses. Specifically, odds ratios are significantly increased for usual employment in several industries (construction, chemical, metal, and transportation) for males and the clerical occupations for females. In addition, there are several associations suggested by increased odds ratios, which are not statistically significant. For males, an increased risk is suggested for occupations in the structural category and employment in industries related to oil and gas extraction (SIC 13), petroleum refining (SIC 60–69), and shipbuilding (SIC 373). For females, occupations in the service category and industries in the other manufacturing group are associated with fairly stable increased odds ratios.

Future analysis of these data will examine the possible interaction of smoking with occupational and industrial groups and a possible need to employ more specific smoking strata. Examination of odds ratios for smoking strata within occupational and industrial categories suggested that an ever/never smoking classification would be sufficient to control for the confounding effect of smoking in the examination of overall risks associated with usual employment in specific occupational and industrial categories as presented here. However, this broad classification may not be sufficiently specific for an examination of interaction of smoking with workplace exposures. In these analyses the classification of "exposed" within a specific category is based upon the "usual" occupation or industry of employment rather than "ever employed" in a given work environment. The use of the usual pattern may be more conservative in the detection of occupational and industrial associations and is perhaps the more appropriate designation to use for a preliminary examination of the data. As noted, the use of the usual occupation and industry of employment did introduce some special constraints on the analysis of the female patterns in that the usual occupation and industry for over

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60% of the cases and controls was "Housewife." We will employ a number of more specific designations of occupational and industrial variables in future analyses.

Even with these recognized limitations, the suggestion which clearly emerges from our data is that there may be a wider variety of workplace exposures associated with substantial increments in the risk of lung cancer than currently recognized. In addition, use of the full work history, including dates will surely aid in refining the preliminary associations reported here.

The relationship of lung cancer cell type with age at time of diagnosis warrants further scrutiny in that the highest odds ratios for the smoking variables were observed for the youngest age group (< 57 years at time of diagnosis). The lack of a "passive smoking" effect when the confounding effect of smoking of individual study subjects is considered, is not consistent with early reports. Although subsequent reports are also not consistent with regard to this association, it may be that the study population available was not sufficiently large to detect a fairly low level effect and that this association needs to be assessed in a considerably larger study population.

These preliminary analyses demonstrate a strong and consistent smoking effect in males and females for all types of lung cancer. The risk differentials associated with cigarette smoking observed for adenocarcinoma and other lung cancer cell types are striking and consistent with findings of others (11). In addition, they reemphasize earlier suggestions that perhaps specific environmental exposures are more strongly associated with specific types of lung cancer. In addition, these data suggest that perhaps lung cancer is more similar in males and females than previously regarded and that the observed differentials in risk by sex are principally due to exposure differentials.

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The authors thank Drs. Irene Easling and Keith Burau and their capable and dedicated staff for their invaluable assistance with the data collection and data management for this study. We also wish to acknowledge the valuable consultation and assistance of Dr. Robert Hardy (UTSPH), Dr. Reuel A. Stallones (UTSPH), Dr. David T. Carr (M.D. Anderson Hospital and Tumor Institute), Dr. S. Donald Greenberg (Baylor College of Medicine), the staff of the Texas State Health Department Statewide Cancer Reporting Program and Bureau of Vital Statistics, and the American Lung Association, San Jacinto Chapter. And lastly, we wish to acknowledge the assistance of the many hospitals, physicians, agencies, and individuals without whom it would not have been possible for us to successfully complete this study.

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Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P., "The Effect of Environmental Tobacco Smoke in Two Urban Communities in the West of Scotland," ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds. R. Rylander, Y. Peterson and M.-C. Snella, European Journal of Respiratory Diseases, Supplement 133(65): 121-126, 1984.

Although this Scottish cohort study included 16,171 individuals, the number of nonsmoking lung cancer cases and controls who reported exposure to ETS was very small. For instance, for males, there were 2 lung cancer deaths among 517 controls and 4 among 310 cases; for females, these numbers were 2 of 523 and 6 of 1394, respectively. Despite these extremely small sample sizes, the authors claim that their data support a dose-response relationship in males.

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ETS – Environmental Tobacco Smoke

Report from a workshop on effects and exposure levels March 15-17, 1983, Geneva, Switzerland

Editors: R. Rylander, Y. Peterson
M.-C. Snella

European Journal of Respiratory Diseases

Supplement No.133, Vol. 65, 1984

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Preface

The Second Workshop on Environmental Tobacco Smoke with particular reference to effects and exposure levels was held in Geneva, Switzerland, March 15-17, 1983.

The workshop was organized by Ragnar Rylander M. D, University of Gothenburg, Sweden, and University of Geneva, Switzerland, together with Yvonne Peterson and Marie-Claire Snella, research assistants and Isabelle Gourdon. It was supported by a grant from the Tobacco Institute, Washington D. C., to the University of Geneva. The symbol for the workshop was designed by Ariane Catry.

The participants in the Workshop are listed below.

Domingo M. Aviado
Toxicological Health Sciences, Inc.
P O Box 307
Short Hills, New Jersey 07078 — USA

Björn Bake
Department of Clinical Physiology
Sahlgren's Hospital
413 45 Gothenburg — SWEDEN

Anthony M. Cosentino
St. Mary's Hospital and Medical Center
450 Stanyan Street
San Francisco, California 94117 — USA

Melvin W. First
Department of Environmental Health Sciences
Harvard University
665 Huntington Avenue
Boston, Massachussets 02115 — USA

Charles R. Gillis
Greater Glasgow Health Board
West of Scotland Cancer Surveillance Unit
Ruchill Hospital
Glascow, G20 9NB — SCOTLAND

Roger Guillerm
Centre d'Etudes et de Recherches
Techniques sous-marines D.C.A.N.
83800 Toulon Naval — FRANCE

Patrick G. Holt
Clinical Immunology Research Unit
Princess Margaret Children's Medical Research Foundation
c/o Princess Margaret Hospital for Children
G P O Box 184 D
Perth, Western Australia — AUSTRALIA

Horst Huckauf
Freie Universitat Berlin
Universitätsklinikum Steglitz
Med Klinik und Poliklinikum
Hindenburgdamm 30
1000 Berlin 45 — WEST GERMANY

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Martin J. Jarvis
Institute of Psychiatry
Addiction Research Unit
101 Denmark Hill
London SE5 8AF — ENGLAND

Roger A. Jenkins
Bio/Organic Analysis Section
Analytic Chemistry Division
Oak Ridge National Laboratory
P O Box X
Oak Ridge, Tennessee 37820 — USA

Michael D. Lebowitz
Division of Respiratory Sciences
The University of Arizona
Health Sciences Center 2
College of Medicine
Tucson, Arizona 84724 — USA

Cornelius J. Lynch
Franklin Institute
Policy Analysis Center
1320 Fenwick Lane
Silver Spring, Maryland 20910 — USA

Göran Pershagen
National Institute of Environmental Medicine
Box 60208
104 01 Stockholm — SWEDEN

Michael A. H. Russell
Institute of Psychiatry
Addiction Research Unit
101 Denmark Hill
London SE5 8AF — ENGLAND

Theodor D. Sterling
Simon Fraser University
Department of Computing Science: 291-4277
Burnaby, British Colombia — CANADA
V5A 1S6

Annetta Weber
Department of Hygiene and Work Physiology
ETH-Zentrum
8092 Zürich — SWITZERLAND

Andreas Zober
Institute for Occupational and Social Medecine and Policlinic for Occupational Diseases
University of Erlangen-Nürnberg
Schillerstr. 25/29, 8520 Erlangen —
WEST GERMANY

ORGANIZING COMMITTEE

Ragnar Rylander
Department of Environmental Hygiene
University of Gothenburg
P O Box 33031
400 33 Gothenburg — SWEDEN

Yvonne Peterson
Department of Environmental Hygiene
University of Gothenburg
P O Box 33031
400 33 Gothenburg — SWEDEN

Marie-Claire Snella
Environmental Medicine Unit
Institute for Social and Preventive Medicine
Quai Charles-Page 2?
1205 Geneva — SWITZERLAND

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3.6. The effect of environmental tobacco smoke in two urban communities in the west of Scotland

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CHARLES R. GILLIS, DAVID J. HOLE, VICTOR M. HAWTHORNE AND PETER BOYLE

INTRODUCTION

The question of whether environmental tobacco smoke (ETS) can damage health has not yet been clearly answered. It is known that a lighted cigarette emits more sidestream smoke than mainstream and that the smoke available for involuntary inhalation contains substantial amounts of carbon monoxide, tar, nicotine, benzo(a)pyrene and other carcinogens, and oxides of nitrogen (1).

Studies from Japan (2) and Greece (3) have suggested that non-smoking wives of heavy smokers have a two-fold increased risk of lung cancer when compared with non-smoking wives of non-smokers. In contrast, analysis of data from the prospective study of the American Cancer Society volunteers (4) has suggested that very little, if any, increased risk of lung cancer exists when non-smoking women married to smoking husbands and non-smokers married to non-smoking husbands are compared.

The present study has been carried out in a defined population group in an area of high incidence (5) of lung cancer with a precisely defined population base. It reports lung cancer data on both males and females.

MATERIALS AND METHODS

The study comprises 16,171 apparently healthy individuals aged between 45 and 64, resident in Renfrew and Paisley, two urban areas in the West of Scotland. They took part in a multiphasic screening survey for cardiorespiratory disease between 1972 and 1976. This represented a response rate of 80% of those randomly sampled from the resident population. Details of this survey have been described by VMH (6). Information on each respondent's smoking habits and their experience of symptoms of respiratory and cardiovascular disease were collected using a self-completed questionnaire, carefully checked at the time of attendance at the screening unit.

The diagnosis of cancer in each individual has been checked in the West of Scotland Cancer Registry and follow up for mortality carried out by record linkage (7) with data from the Registrar General for Scotland. Follow up is complete until 31 December 1982.

As members of the same household attended the screening unit, it was possible to identify smoking and non-smoking partners of smokers and non-smokers. These were allocated to categories defined so as to represent an increasing measure of tobacco exposure.

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TABLE 1. *Number and percentage of individuals by category.*
Number of individuals attending screening = 16,171
Number within partnerships screened = 8,128 (ex-smokers excluded)

Category	Male N	Male %	Female N	Female %
Controls	517	12.7	523	12.9
ETS exposure	310	7.6	1394	34.3
Smoking	1395	34.3	310	7.6
Smoking + ETS exposure	1845	45.4	1834	45.2
Total	4067	100	4061	100

TABLE 2. *Age standardized prevalence of self-reported respiratory symptoms by category. Per cent of all within each group. Males*

Respiratory symptom	Controls	ETS exposure	Smoking	Smoking + ETS exposure
Infected spit	3.3	4.2	11.1	12.5
Persistent spit	10.1	14.5*	33.9	35.6
Dyspnoea	7.4	11.9*	14.0	15.4
Hypersecretion	7.2	11.9*	20.6	21.6
Number of individuals	517	310	1395	1845

*P value < 0.05 for comparison of control and ETS exposure group

TABLE 3. *Age standardized prevalence of self-reported respiratory symptoms by category. Per cent of all within each group. Females*

Respiratory symptom	Controls	ETS exposure	Smoking	Smoking + ETS exposure
Infected spit	2.1	2.8	10.0	9.1
Persistent spit	6.3	7.2	23.9	23.1
Dyspnoea	9.7	14.7**	16.2	18.3
Hypersecretion	3.9	4.8	17.6	17.1
Number of individuals	523	1394	310	1834

**P value < 0.01 for comparison of control and ETS exposure group

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1. Control—an individual who does not smoke and who lives at the same address as another individual who does not smoke.
2. ETS exposed—an individual who does not smoke but who lives at the same address as another individual who does smoke.
3. Smoker—an individual who is a smoker or who has given up smoking up to five years ago but who lives at the same address as an individual who does not smoke.
4. Smoker and ETS exposed—an individual who is or who has been a smoker up to five years ago and who lives at the same address as an individual who also smokes.

All individuals in these categories were aged 45-64 at the time of the survey. Ex-smokers who had given up smoking for five years or more have been excluded from this analysis.

RESULTS

The number of males and females in each of the categories defined above is shown in Table 1. 97.6% of the pairings were male/female partnerships.

The prevalence of self-reported respiratory symptoms (6) found at the survey is shown for each category for males in Table 2 and for females in Table 3. For each measure, infected spit, persistent spit, dyspnoea and hypersecretion an increasing dose response relationship was evident in males. The prevalence of these four symptoms was slightly higher in the exposed to ETS than in the controls. This observation was consistent in both males and females.

The prevalence of cardiovascular symptoms found at the time of the survey is shown in Table 4. In females angina and ECG abnormalities (6) were slightly more common in the group exposed to ETS than in the controls, although the magnitude of the differences was small. The reverse trend was shown for males.

Male mortality for the different categories is shown in Table 5. A dose-response relationship was found for lung cancer rising from a rate of 4 per 10,000 for the control group to 13 per 10,000 for the group exposed to ETS to 22 per 10,000 for the smoking group and 24 per 10,000 for the smoking group also exposed to ETS. The rates for other smoking related cancers and for smoking related diseases (8) did not show a difference between the control and groups exposed to ETS except for the rate for myocardial infarction (ICD410) which was

TABLE 4. *Age standardised prevalence of cardiovascular symptoms by category. Per cent of all within each group*

Cardiovascular symptom	Controls	ETS exposure	Smoking	Smoking + ETS exposure
Males:				
Angina	6.6	6.4	9.6	12.3
Major ECG abnormality	1.4	1.3	2.0	2.2
Females:				
Angina	4.2	5.3	5.4	6.1
Major ECG abnormality	0.4	0.6	0.6	0.5

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TABLE 5. *Annual age standardised mortality rates per 10,000 by smoking category Males*

Cause of death	Controls	ETS exposure	Smoking	Smoking + ETS exposure
All causes	91	90	156	156
Lung ca	4(2)	13(4)	22(30)	25(44)
Other Ca	12(6)	6(2)	24(34)	22(41)
MI (410)	31(16)	45(14)	60(84)	46(84)
IHD (411-4)	4(2)	0(0)	11(15)	14(25)
CVD	10(5)	3(1)	12(17)	16(29)
Others	31(16)	23(7)	27(38)	35(64)
Smoking related	75(39)	77(24)	140(195)	134(247)
Non-smoking related	16(8)	13(4)	17(23)	22(40)
Total number of deaths	47	28	218	287

Figures in parenthesis are the numbers of deaths

TABLE 6. *Annual age standardised mortality rates per 10,000 by smoking category Females*

Cause of deaths	Controls	ETS exposure	Smoking	Smoking + ETS exposure
All causes	40	58	87	77
Lung Ca	4(2)	4(6)	7(2)	6(11)
Other Ca	19(10)	24(33)	26(8)	22(40)
MI (410)	4(2)	12(17)	19(6)	21(39)
IHD (411-4)	0(0)	1(2)	3(1)	2(4)
CVD	2(1)	4(5)	7(2)	9(16)
Others	12(6)	13(18)	26(8)	17(31)
Smoking related	15(8)	30(42)	55(17)	52(96)
Non-smoking related	23(12)	27(37)	36(11)	24(44)
Total number of deaths	21	81	27	141

Figures in parenthesis are the numbers of deaths

TABLE 7. *Percentage smoking 15 or more cigarettes per day*

	Controls	ETS exposure	Smoking	Smoking + ETS exposure
Males	0	0	41.8	57.3
Females	0	0	46.5	53.4

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slightly higher in the group exposed to ETS than in the controls.

Female mortality is shown in Table 6. All causes mortality is higher in the group exposed to ETS than in the controls. This was not the case for lung cancer although mortality from myocardial infarction was higher in the group exposed to ETS when compared with the controls.

Division of all diseases into those considered smoking and non-smoking related (8) produced a higher rate in the group exposed to ETS when compared with controls.

On account of the apparently unusual relationship between lung cancer risk and tobacco consumption in the West of Scotland (9) the amount smoked by individuals in the defined categories is shown in Table 7. In the smoking group also exposed to ETS 57.3 % of males and 53.4 % of females smoked more than 15 cigarettes per day. This compares with 41.8 % of males and 46.5 % of females in the smoking group.

DISCUSSION

Insufficient time has elapsed since the completion of the recruitment phase of this study (1976) for sufficient numbers, either of incident cases of cancer or of other diseases, to allow firm conclusions to be based on the results. The results have been expressed as annual age standardised rates per 10,000, as the total number of incident cases and the number of deaths is small in the control and ETS exposure groups (Tables 5, 6).

The results relate to only 8,128 of the 16,171 individuals who attended the multi-phasic screening unit (50 %). Some of this discrepancy can be accounted for by those living alone, those living with a partner outwith the age range, and those living with a partner who has not attended. Those who have been exsmokers for five years or more were also excluded from the analysis. As there is still doubt whether these groups account for the total discrepancy, given an initial response rate of 80 %, the authors require to continue their investigation of this apparent discrepancy.

This study has unique features which allow even preliminary results to be of interest.

These are:

1. The study has been carried out in an area with the highest national incidence rate of lung cancer recorded (5).
2. It is a prospective cohort study carried out in a geographically defined population whose members are homogeneous by social class and ethnic group.
3. Other reports (2, 3, 4) concentrate on females. This study includes both sexes.
4. No questions concerning exposure to ETS were asked, thus avoiding the bias inherent in self-reported assessments of partnership dosage.

Given the strength of the epidemiological association between cigarette smoking and lung cancer, it is this disease rather than ischaemic heart disease that would be first to appear in excess in the cohort if a dose response relationship existed, especially as the respondents were all apparently healthy at the time of screening.

In males, the cases of lung cancer occurring in non-smokers were found more frequently in those exposed to ETS (4/310) than in the controls (2/517) (Table 5). No dose-response relationship was apparent in females for lung cancer deaths though an effect was present when all smoking related (8) deaths including deaths from myocardial infarction were taken into account (Table 6).

These findings may be supported to an extent by the dose-response relationship that exists for self-reported respiratory symptoms

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(Tables 2, 3), all of which are more frequently reported in the group exposed to ETS than in the controls and four of which achieve statistical significance.

The number of deaths in the control and ETS exposure groups is very small and may explain the lack of an apparent dose-response in females. However, as the relative risk for lung cancer for active smokers is much higher in males than females it may be too early to expect many females in the ETS exposure group to be affected. This would also apply to male as well as female deaths from myocardial infarction.

Occupation has not been taken into account in this analysis, as its effect on lung cancer risk in non-smokers is thought to be marginal (4, 10).

The West of Scotland is a valuable area to continue examination of the effect of ETS on account of the relatively high rate of lung cancer in non-smokers and the flattening of the dose-response relationship above an average consumption of 20 cigarettes per day (9).

In conclusion, the clear dose-response relationship with lung cancer observed in males exposed to ETS supports observations from previous studies. Although the number of deaths on which the current analysis is based is small. The nature of the findings makes continuation of this study important.

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Charles R. Gillis
Greater Glasgow Health Board
West of Scotland Cancer Surveillance Unit
Auchill Hospital
Glasgow, G20 9NB, SCOTLAND.

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Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M., "Passive Smoking and Cardiorespiratory Health in a General Population in the West of Scotland," British Journal of Cancer 299: 423-427, 1989.

This publication reports additional information on the cohort study first published as Gillis, et al., 1984. From a group of 7,997 persons, 243 males and 1295 females were classified as exposed to cigarette smoke from a cohabitant. The cohabitant was also interviewed along with the case. There were 428 male and 489 female controls (individuals who had never smoked and whose cohabitant had never smoked).

The RR of 2.41 (95% CI 0.45-12.83) presented for lung cancer is adjusted for age, sex, social class and cardiovascular variables. The very wide confidence interval reflects the fact that the estimate is based on only seven lung cancer deaths among cases and two deaths among controls.

The authors claim that their study provides evidence for increased mortality from all causes among persons exposed to ETS. However, their point estimates are not statistically significant.

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Passive smoking and cardiorespiratory health in a general population in the west of Scotland

David J Hole, Charles R Gillis, Carol Chopra, Victor M Hawthorne

Abstract

Objective—To assess the risk of cardiorespiratory symptoms and mortality in non-smokers who were passively exposed to environmental smoke.

Design—Prospective study of cohort from general population first screened between 1972 and 1976 and followed up for an average of 11·5 years, with linkage of data from participants in the same household.

Setting—Renfrew and Paisley, adjacent burghs in urban west Scotland.

Subjects—15 399 Men and women (80% of all those aged 45-64 resident in Renfrew or Paisley) comprised the original cohort; 7997 attended for multiphasic screening with a cohabitee. Passive smoking and control groups were defined on the basis of a lifelong non-smoking index case and whether the cohabitee had ever smoked or never smoked.

Main outcome measure—Cardiorespiratory signs and symptoms and mortality.

Results—Each of the cardiorespiratory symptoms examined produced relative risks >1·0 (though none were significant) for passive smokers compared with controls. Adjusted forced expiratory volume in one second was significantly lower in passive smokers than controls. All cause mortality was higher in passive smokers than controls (rate ratio 1·27 (95% confidence interval 0·95 to 1·70)), as were all causes of death related to smoking (rate ratio 1·30 (0·91 to 1·85)) and mortality from lung cancer (rate ratio 2·41 (0·45 to 12·83)) and ischaemic heart disease (rate ratio 2·01 (1·21 to 3·35)). When passive smokers were divided into high and low exposure groups on the basis of the amount smoked by their cohabitees those highly exposed had higher rates of symptoms and death.

Conclusion—Exposure to environmental tobacco smoke cannot be regarded as a safe involuntary habit.

Introduction

Though evidence has accumulated about the risk to health of involuntary, or passive, exposure to environmental tobacco smoke, further information is required from cohort studies to confirm these observations. Deleterious effects on the respiratory system of infants and children have been observed[1,2] as have chronic effects on lung function in adults,[3,4] but these findings have been criticised on methodological grounds.[5] An overview of 10 case-control and three cohort studies estimated a relative risk of 1·35 for lung cancer in people passively exposed compared with non-exposed controls.[6] Three studies have reported increased (though not significant) risks of ischaemic heart disease in non-smokers with partners who smoke.[7-9] Problems in interpreting these findings include lack of an objective measure of dose or exposure, failure to adjust for confounding variables, inappropriate methods of statistical analysis, and failure to measure other potentially important variables.[10]

This report is based on the Renfrew-Paisley survey, which was carried out in an area with a high incidence of lung cancer; it overcomes many of these criticisms. The survey prospectively studied a general population aged 45-64 years, and the collected data allowed participants from the same household to be identified. The measure of exposure to environmental tobacco was obtained directly from cohabitees and did not rely on self reporting. Data on prevalences of symptoms of respiratory and cardiovascular disease, forced expiratory volume in one second, mortality, and incidence of cancer are all available for this population. The findings reported here update an earlier report; it adds 567 further deaths to the previous findings[11] and extends the range of baseline measurements to include forced expiratory volume in one second. Confounding variables such as social class, blood pressure, cholesterol concentration, body mass index, and social class have been allowed for in calculating relative risks for passive smokers.

Subjects and methods

This general population cohort comprises all men and women aged 45-64 years resident in the towns of Renfrew and Paisley in the west of Scotland between 1972 and 1976.[12] Eligibility was established by a door to door census of all households in the two towns. Everyone who met the age and residency criteria was invited to attend one of 12 temporary centres for a multiphasic cardiorespiratory screening examination.[11] Between 1972 and 1976, 15 399 residents (an 80% response) completed a standardised self administered questionnaire that included questions on smoking behaviour and was checked by experienced interviewers when subjects attended for screening. Respiratory symptoms were assessed with the Medical Research Council's bronchitis questionnaire. By identifying participants from the same household it was possible to study varying exposures to tobacco smoke in a subsample of 3960 men and 4037 women and to calculate relative risks for a range of cardiorespiratory variables including mortality.

Four groups, in which the index case was aged 45-64 at the time of the survey, were defined based on the index case and on the cohabitees ever or never having smoked.

(1) Control: the index case had never smoked and lived at the same address as another subject who had never smoked. No one else in the household who attended for screening was a smoker or ex-smoker.

(2) Passive smoking: the index case had never smoked and lived at the same address as a subject wh had.

(3) Single smoking: the index case was a smoker or ex-smoker and lived at the same address as a subject who had never smoked. No one else in the household who attended for screening was a smoker or ex-smoker.

(4) Double smoking: the index case was a smoker or ex-smoker who lived at the same address as a subject who was also a smoker or ex-smoker.

If the index cases were ex-smokers they were classified as single smokers or double smokers depending on whether the cohabitees had never smoked or

West of Scotland Cancer Surveillance Unit, Ruchill Hospital, Glasgow G20 9NB
David J Hole, MSC, *statistician*
Charles R Gillis, MD, *director*

Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, United States
Carol Chopra, *research student*
Victor M Hawthorne, MD, *professor*

Correspondence and requests for reprints to: Mr Hole.

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ever smoked. If the cohabitees were ex-smokers the index cases were classified as passive smokers if they had never smoked or as double smokers if they had ever smoked. Thus the controls represent a group whose passive exposure was as low as possible within the constraints of the study design. Results for the two active smoking groups have been included to give some indication of dose-response and provide a perspective for any differences found between the control and passive smoking groups.

A cohabitee was defined as a respondent sharing the same household environment and examined at the same time in the survey as the index case. Some households contained cohabitees of the same sex. Some of the subjects who were examined were above or below the age range eligible for inclusion in the study. These subjects were not analysed as index cases but information on their smoking behaviour as cohabitees was used as the measure of passive exposure for eligible index cases.

Mortality data was obtained from the National Health Service central register and the General Register Office for Scotland. Incidence of cancer was obtained through the cancer registry system and used to verify that the classification on the death certificate was the same as that received by the registry. Data presented are complete to the end of December 1985, an average follow up of 11·5 years.

Prevalences for respiratory and cardiovascular symptoms were standardised for age and sex using the age and sex distribution of the whole cohort as standard. Similarly, mortality was standardised for age and sex using life tables to estimate survival at 11 years of follow up.[14]

Mean forced expiratory volumes in one second for the four exposure groups were adjusted for age, height, and sex by determining the best fit set of parallel regression models for forced expiratory volume in one second as a linear function of age and height for men and women separately in each group. The mean adjusted forced expiratory volume in one second for each group was then calculated for the average age and height of men and women separately, and a weighted average (corresponding to the proportion of men and women) was computed. Probability values were obtained from the analysis of variance.

Estimates of relative risk and 95% confidence intervals for passive smokers compared with controls were adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol concentration and body mass index (weight (kg)/(height (m))^2 × 100) using the logistic regression model[15] for cardiorespiratory symptoms and Cox's proportional hazards model for mortality.[16] Levels of significance were derived from the partial likelihood function.[17] The biomedical data processing programs (BMDP) package was used to compute estimates of risk and levels of probability.[18]

A supplementary questionnaire in two of the 12 centres in which the survey was carried out asked subjects the extent to which they were exposed to cigarette smoke from any other person in the household, irrespective of whether these people were eligible for or attended the survey, and also in their work environment.

TABLE I—*Composition of groups exposed to cigarette smoke*

	No (%) of men (index cases)	No (%) of women (index cases)	Total
Controls (neither index case nor cohabitee ever smoked)	428 (10·8)	489 (12·1)	917
Passive smoking (only cohabitee ever smoked)	243 (6·1)	1295 (32·1)	1538
Single smoking (only index case ever smoked)	1420 (35·9)	331 (8·2)	1751
Double smoking (both index case and cohabitee ever smoked)	1869 (47·2)	1922 (47·6)	3791
Total	3960 (100)	4037 (100)	7997

TABLE II—*Social class of men in groups exposed to cigarette smoke. Figures in parentheses are percentages*

Social class	Exposure group: Controls	Passive smoking	Single smoking	Double smoking
I	23 (5·4)	13 (5·3)	61 (4·3)	78 (4·2)
II	85 (19·9)	37 (15·2)	225 (15·8)	235 (12·6)
III non-manual	63 (14·7)	23 (9·5)	197 (13·9)	204 (10·9)
III manual	157 (36·7)	96 (39·5)	538 (37·9)	771 (41·3)
IV	80 (18·7)	59 (24·3)	315 (22·2)	438 (23·4)
V	17 (4·0)	11 (4·5)	68 (4·8)	122 (6·5)
Insufficient information	3 (0·7)	4 (1·6)	16 (1·1)	21 (1·1)
Total	428 (100·1)	243 (99·9)	1420 (100)	1869 (100)

Results

The number of men and women in the four exposure groups is shown in table I. Passive smokers comprised

TABLE III—*Smoking habit of cohabitees in passive smoking and double smoking groups. Figures are percentages (numbers)*

No of cigarettes smoked per day by cohabitee	Index case: Men: Passive smoking group	Men: Double smoking group	Women: Passive smoking group	Women: Double smoking group
1-14	31·3 (76)	30·0 (561)	15·1 (196)	11·4 (219)
≥15	46·1 (112)	52·7 (985)	41·8 (541)	56·2 (1080)
15-24	42·0 (102)	45·9 (858)	30·8 (399)	37·1 (713)
≥25	4·1 (10)	6·8 (127)	11·0 (142)	19·1 (367)
Ex-smoker	22·6 (55)	17·3 (323)	43·1 (558)	32·4 (623)

TABLE IV—*Age and sex standardised rates of respiratory and cardiovascular symptoms related to exposure to cigarette smoke. Numbers of index cases with symptoms are given in parentheses*

	Exposure group: Controls (n=917)	Passive smoking (n=1538)	Single smoking (n=1751)	Double smoking (n=3791)
Respiratory symptoms:				
Infected sputum	2·3 (22)	3·3 (44)	10·5 (189)	10·5 (396)
Persistent sputum	7·8 (72)	9·9 (122)	28·0 (541)	28·7 (1079)
Dyspnoea	10·1 (95)	12·2 (197)	13·4 (229)	16·6 (618)
Hypersecretion	5·3 (48)	6·9 (81)	17·6 (327)	18·3 (681)
Cardiovascular symptoms:				
Angina	4·6 (43)	4·7 (74)	7·7 (165)	9·1 (334)
Major abnormality found on electrocardiogram	1·0 (8)	1·1 (13)	1·4 (31)	1·5 (49)
Mean forced expiratory rate in one second (l):				
Unadjusted	2·32	2·21	2·12	2·09
Adjusted	2·31	2·23	2·12	2·07

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TABLE V- *Age and sex adjusted mortality per 10 000 per year by category of exposure to cigarette smoke. Figures in parentheses are actual numbers of deaths*

	Controls	Passive smoking	Single smoking	Double smoking
All causes	83·1 (99)	97·4 (164)	160·0 (420)	155·6 (734)
Lung cancer	1·6 (2)	5·0 (7)	23·2 (54)	21·4 (93)
Ischaemic heart disease	27·3 (30)	47·7 (54)	61·0 (171)	60·7 (260)
All causes of death related to smoking	60·8 (71)	72·2 (104)	130·4 (362)	129·9 (592)

TABLE VI—*Age adjusted prevalence of respiratory and cardiovascular symptoms and age standardised mortality per 10 000 per year for women in control and passive smoking groups. Figures in parentheses are numbers of actual cases*

	Controls (n=489)	Passive smokers: Low exposure (n=754)	Passive smokers: High exposure (n=541)
	Prevalence		
Respiratory symptoms:			
Infected sputum	2·1 (10)	2·4 (18)	3·1 (17)
Persistent sputum	6·4 (31)	5·8 (45)	8·6 (46)
Dyspnoea	12·7 (60)	11·2 (84)	16·2 (88)
Hypersecretion	4·1 (19)	3·8 (29)	5·7 (30)
Cardiovascular symptoms:			
Angina	3·6 (17)	4·1 (32)	5·8 (31)
Major abnormality found on electrocardiogram	0·4 (2)	1·1 (8)	0·5 (2)
	Mortality		
All causes	58·3 (32)	64·6 (70)	87·8 (54)
Lung cancer	3·2 (1)	2·5 (2)	5·7 (3)
Ischaemic heart disease	6·8 (3)	14·2 (14)	28·0 (16)
All causes of death related to smoking	34·9 (17)	35·2 (39)	47·3 (30)

6·1% (243/3960) of men and 32·1% (1295/4037) of women. Of the cohabitees, 91·6% (7325) were of the opposite sex. The composition of the groups by social class is shown in table II.

The extent of passive exposure experienced by passive smokers in relation to subjects in the double smoking group is shown in table III. In all, 46·1% (112) men and 41·8% (541) women in the passive smoking group lived in households where the cohabitee was smoking 15 or more cigarettes a day. This compared with 52·7% (985) men and 56·2% (1080) women in the double smoking group. Ex-smokers were more common in households in which the index case had never smoked.

The prevalence of signs and symptoms for the four exposure groups is shown in table IV. For each of the four respiratory measures (infected sputum, persistent sputum, dyspnoea, and hypersecretion) the rates in the control group were lower than those in the passive smoking group and considerably lower than in the single and double smoking groups. The rates for angina and major abnormalities found on electrocardiography were similar in the control and passive smoking groups and lower than in the active smoking groups.

Mean forced expiratory volumes in one second adjusted for sex, age, and height were significantly higher ($p<0·01$) in controls than in those passively exposed to cigarette smoke and were significantly higher than among active smokers.

Mortality adjusted for age and sex in the four groups is presented in table V. Total mortality was higher among passive smokers than controls. This was reflected in the category of all causes of death related to smoking and was highest for ischaemic heart disease. Lung cancer mortality was higher among passive smokers than controls, but the number of deaths involved was small.

The supplementary questionnaire on exposure to cigarette smoke at home and work allowed a check to be made of the smoking habits of other household members who were not part of the survey. A regular smoker living in the same household was reported by 5% (2/44) of controls compared with 69% (27/39) of passive smokers. Of women, 21% (13/62) of controls lived in households with a regular smoker compared with 63% (125/197) of passive smokers.

Women reported that most of their passive exposure was at home rather than at work, which suggested that they were the appropriate group in which to examine whether there was a dose-response relation. A high exposure passive smoking group was therefore defined as women whose cohabitee was smoking 15 or more cigarettes daily, and the remaining female passive smokers were defined as a low exposure group. Table VI presents the age standardised rates for respiratory and cardiovascular symptoms and mortality for the control and the low and high exposure passive smoking groups. For each of the four respiratory symptoms the highly exposed passive smokers had rates that were higher than those in passive smokers whose exposure was low and those in the controls. There were no consistent differences between the low passive exposure group and the controls. A similar pattern was found for angina but not for major abnormalities detected by electrocardiography.

The adjusted forced expiratory volume at one second was significantly lower in passive smokers with high exposure compared with those with low exposure (mean 1·831 *v* 1·891; $p<0·05$). No significant difference was found between passive smokers with low exposure and controls (1·891 *v* 1·881). Age adjusted mortality was increased for the passive smokers with high exposure compared with low and with controls for all cause mortality, all cause mortality related to smoking, ischaemic heart disease, and lung cancer.

Table VII shows the adjusted relative risks for passive and active smokers compared with controls. For each variable the relative risk associated with passive smoking was >1·0. The confidence interval included 1·0 except for ischaemic heart disease, for which the estimate of risk was significantly different from unity ($p=0·008$).

Table VIII shows the relative risks for double smokers compared with single smokers after additional adjustment for quantity smoked. Dyspnoea was signi-

TABLE VII—*Relative risks associated with passive smoking adjusted for age, sex, and social class and for cardiovascular variables, diastolic blood pressure, serum cholesterol concentration, and body mass index*

	Relative risk (passive smokers compared with controls)	95% Confidence interval	p Value	Relative risk (active smokers compared with controls)
Respiratory symptoms:				
Infected sputum	1·34	0·76 to 2·36	0·3	4·53
Persistent sputum	1·19	0·85 to 1·67	0·3	4·49
Dyspnoea	1·09	0·82 to 1·45	0·5	1·60
Hypersecretion	1·21	0·81 to 1·82	0·3	3·77
Cardiovascular symptoms:				
Angina	1·11	0·73 to 1·70	0·6	1·89
Major abnormalities found on electrocardiogram	1·27	0·48 to 3·35	0·6	1·51
Mortality:				
All causes	1·27	0·95 to 1·70	0·10	2·07
All causes of death related to smoking	1·30	0·91 to 1·85	0·15	2·33
Ischaemic heart disease	2·01	1·21 to 3·35	0·008	2·27
Lung cancer	2·41	0·45 to 12·83	0·3	10·64

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TABLE VIII—*Relative risks in double smokers compared with single smokers, adjusted for age, sex, amount smoked, and social class and for cardiovascular variables, diastolic blood pressure, serum cholesterol concentration, and body mass index*

	Relative risk	95% Confidence interval	p Value
Respiratory symptoms:			
Infected sputum	0·96	0·79 to 1·16	0·65
Persistent sputum	1·06	0·92 to 1·21	0·45
Dyspnoea	1·25	1·05 to 1·49	0·02
Hypersecretion	1·02	0·87 to 1·20	0·75
Cardiovascular symptoms:			
Angina	1·17	0·95 to 1·44	0·15
Major abnormalities found on electrocardiogram	1·11	0·68 to 1·79	0·65
Mortality:			
All causes	1·01	0·87 to 1·18	0·9
All causes of death related to smoking	0·99	0·84 to 1·16	0·9
Ischaemic heart disease	0·89	0·72 to 1·11	0·3
Lung cancer	1·13	0·79 to 1·63	0·5

ficantly more common among double smokers (p=0·02), and though none of the other variables was significant, six had risks >1·0.

Discussion

Whether inhaling other people's tobacco smoke is a risk factor for lung cancer and other diseases related to smoking is now under serious scientific consideration. Studies of the concentrations of cotinine in the urine and saliva of passive smokers suggest that the dose received may be equivalent to smoking up to three cigarettes a day.[9] Though sidestream smoke contains different proportions of chemical constituents than does mainstream smoke and the same dose received passively might not translate directly to the same risk as in active smokers, the risks expected for passive smokers will probably be of a similar magnitude to those found in active smokers of up to three cigarettes daily; consequently, only very large studies will have sufficient power to detect such risks. A meta-analysis is currently the only way to establish precise estimates of risk, and it is essential that all studies are included.

This paper updates a previous publication[11] with mortality now extended to an average follow up time of 11·5 years and the control and passive smoking groups redefined to exclude those who smoked only pipes or cigars and those who smoked cigarettes irregularly. The original questionnaire in its coded form did not distinguish pipe and cigar smokers and those who smoked fewer than five cigarettes a day from non-smokers. Written information on the questionnaires allowed this to be clarified, and these additional data were added to the computer files.

The sample size in this study does not provide sufficient statistical power to detect risks of the magnitude expected. Thus the lack of significance should not be the sole criterion of whether a genuine effect may be present. Several findings should be borne in mind when interpreting these results. **Firstly, for each of the 10 measures examined, from respiratory symptoms to causes of mortality, the relative risk was consistently larger than unity. This remained so after adjusting for intervening risk factors such as age, sex, social class, blood pressure, cholesterol concentration, and body mass index.** Secondly, the one measure for which sufficient statistical power was available—that is, forced expiratory volume in one second—gave a significant result. Thirdly, when a group of passive smokers with high exposure was defined there was an increase in the dose-response relation for nine of the 10 variables. Fourthly, in comparison with the relative risks found for the two active smoking groups, each increased risk was biologically plausible, with the possible exception of that for ischaemic heart disease.

The findings for respiratory symptoms are similar to those of other studies: a decreased forced expiratory volume in one second in passive smokers has been found previously,[10] and the risks for lung cancer are consistent with those in the overview by Wald *et al.*[6] Few data relate passive smoking to cardiovascular disease, but a relative risk as high as 2·2 for mortality from ischaemic heart disease in passive smokers has been quoted.[1] Our risk of 2·0 seems large in comparison with that found for active smokers, and the possibility that chance has inflated this risk cannot be excluded, but as the lower 95% confidence limit for the relative risk is greater than one it would appear that chance alone is not responsible for the excess.

When investigating risks close to unity it is important to consider the effect of potential biases. Biases may operate at the time data are collected. Between 1972 and 1976, however, passive smoking was not an issue. Subjects reported their own smoking habits and no self reporting of passive exposure was undertaken. It was not until 1983 that subjects within the same household were linked, and this was carried out without any reference to the measures of outcome examined subsequently.

There is no direct measure available to prove that the passive smokers received a higher environmental dose of tobacco smoke than the controls, but in the supplementary questionnaire that covered the smoking habits of household members irrespective of whether they attended the original survey only 5% of controls said that there was a current smoker in the household, compared with 63% of passive smokers. Greater exposure to tobacco smoke at work supported the idea that passive smokers were more likely than controls to be in contact with environmental tobacco smoke outside the home. This was measured by Wald and Ritchie,[11] who showed that non-smoking husbands of smoking wives had higher urinary cotinine concentrations than non-smoking husbands of non-smoking wives. Our definition of categories of exposure is comparable with that of other studies and would seem to identify groups with different mean levels of passive exposure. The high level of heavy smoking in our cohort[12] might also indicate that this difference is greater than that found in other studies.

The problem of smokers deliberately classifying themselves as non-smokers[13] is a far less serious bias in cohort studies than in case-control studies, because at the interview stage there is no indication which subjects will subsequently die. The likelihood of differential misclassification rates—that is, higher in the passive smoking than in the control group—is debatable as this implies that someone in the double smoking group is more likely to pretend to be a non-smoker than someone in the single smoking group. When the cohabitee is a smoker the reverse may be more likely to be true.

It has been suggested that non-smokers who marry smokers may be different from non-smokers who marry non-smokers.[14] A higher proportion of passive smokers were in social classes III manual, IV, and V, but no differences were found for other possible risk factors such as occupation, raised blood pressure, cholesterol concentration, or body mass index. In any case the final analysis, which estimated the relative risks, adjusted for each of these factors.

The effect of passive smoking on those who already smoke is far harder to isolate. The dose received by active smokers from smoking ranges widely,[15,16] and adding a small extra component due to passive exposure may not lead to much of a difference in mean doses for double smokers compared with single smokers. Hence, the increased risk for double smokers relative to single smokers may be substantially less than that for passive smokers relative to controls. Thus the statistical power of a single study is an important consideration and in the absence of other published data on this aspect it is difficult to interpret our results

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for the effects of passive smoking on smokers. Therefore the main emphasis of this paper is an estimation of the risks of passive smoking in lifelong non-smokers; data are presented for the active smoking groups to provide an estimate of dose-response.

Our results are based on a general population cohort study carried out in an area with a high level of diseases related to smoking. A consistent increase in risk was observed in passive smokers for each of the 10 variables measured covering respiratory symptoms, forced expiratory volume in one second, cardiovascular symptoms, and subsequent mortality, including lung cancer and ischaemic heart disease. A dose-response relation was seen, and the risks were biologically plausible in relation to the size of the risks found for the active smokers. These three factors taken together increase our concern that exposure to other people's tobacco smoke cannot be regarded as a safe involuntary practice.

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Carbohydrate deficient transferrin: a marker for alcohol abuse

A Kapur, G Wild, A Milford-Ward, D R Triger

Abstract

***Objective*—To assess the value of serum carbohydrate deficient transferrin as detected by isoelectric focusing on agarose as an indicator of alcohol abuse.**

***Design*—Coded analysis of serum samples taken from patients with carefully defined alcohol intake both with and without liver disease. Comparison of carbohydrate deficient transferrin with standard laboratory tests for alcohol abuse.**

***Setting*—A teaching hospital unit with an interest in general medicine and liver disease.**

***Patients*—22 "Self confessed" alcoholics admitting to a daily alcohol intake of at least 80 g for a minimum of three weeks; 15 of the 22 self confessed alcoholics admitted to hospital for alcohol withdrawal; 68 patients with alcoholic liver disease confirmed by biopsy attending outpatient clinics and claiming to be drinking less than 50 g alcohol daily; 47 patients with non-alcoholic liver disorders confirmed by biopsy; and 38 patients with disorders other than of the liver and no evidence of excessive alcohol consumption.**

***Intervention*—Serial studies performed on the 15 patients undergoing alcohol withdrawal in hospital.**

***Main outcome measure*—Determination of relative value of techniques for detecting alcohol abuse.**

***Results*—Carbohydrate deficient transferrin was detected in 19 of the 22 (86%) self confessed alcohol abusers, none of the 47 patients with non-alcoholic liver disease, and one of the 38 (3%) controls. Withdrawal of alcohol led to the disappearance of carbohydrate deficient transferrin at a variable rate, though in some subjects it remained detectable for up to 15 days. Carbohydrate deficient transferrin was considerably superior to the currently available conventional markers for alcohol abuse.**

***Conclusion*—As the technique is fairly simple, sensitive, and inexpensive we suggest that it may be valuable in detecting alcohol abuse.**

Introduction

The medical and social consequences of alcohol abuse are major problems throughout the world. Although many people readily acknowledge the extent of their alcohol consumption, others attempt to conceal it, and we lack reliable objective means of identifying surreptitious alcohol consumption. Currently available laboratory markers have considerable limitations, being insensitive, non-specific, or dependent on liver damage. The mean corpuscular volume rises in patients with thyroid disease, folic acid deficiency, and liver disease,[1] whereas serum γ-glutamyltransferase activity is affected by drugs that induce microsomal enzymes as well as rising in all forms of obstructive liver damage.[2] Serum aspartate aminotransferase activity is more commonly raised in alcoholics than alanine aminotransferase activity is, and whereas a ratio of aspartate to alanine aminotransferase activity of greater than 2:1 is strongly suggestive of alcoholic liver disease[3] this is of little value in subjects in whom the

Department of Medicine and Protein Reference Unit, Royal Hallamshire Hospital, Sheffield S10 2JF
A Kapur, BMEDSCI, *medical students*
G Wild, BSC, *senior scientist*
A Milford-Ward, FRCPATH, *director of protein reference unit*
D R Triger, FRCP, *reader in medicine*

Correspondence to:
Dr Triger.

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Nonsmoking cases were extracted from another ongoing case-control study of "tobacco-related cancers"; 37 nonsmoking males and 97 nonsmoking females were identified. A control was matched to each on age, sex, race, hospital, date of interview and nonsmoking status. A further subset of these cases answered questions on "passive smoking" via questionnaire, resulting in a total of 25 male cases, 53 female cases and their matched controls.

Six male cases reported exposure to other people's cigarette smoke at home, compared to 5 controls; for women, the numbers were 16 cases and 17 controls. These numbers were not statistically significantly different. For workplace exposure, in males, 18 of 25 cases and 11 of 25 controls reported cigarette smoke exposure; the difference was marginally statistically significant ($p = 0.05$). In females, no statistically significant difference was reported for workplace exposure (26 of 53 cases vs 31 of 53 controls). In their Discussion, the authors present detailed comments on studies to date (1984) which considered ETS.

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Lung Cancer in Nonsmokers

GEOFFREY C. KABAT, PHD, AND ERNST L. WYNDER, MD

Among 2668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in "validated" nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (relative risk = 3.10, 95% confidence interval 1.11–8.64), but the significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed.

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ALTHOUGH LUNG CANCER risk is strongly associated with cigarette smoking, lung cancer does infrequently occur in nonsmokers.[1,2] Several features distinguish lung cancer in nonsmokers from that occurring in smokers. First, most cases of lung cancer in nonsmokers are found in women.[2,3] Second, the distribution of histologic types of lung cancer differs between smokers and nonsmokers. In smokers the epidermoid type predominates, whereas in nonsmokers adenocarcinoma is more common, especially in women.[2-5]

This article presents data from a case–control study of nonsmoking patients with histologically confirmed diagnoses of primary lung cancer with respect to histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and, to a limited extent, exposure to the tobacco smoke of others. Due to the small number of cases and controls on whom we have information on passive inhalation, the data presented here on that question are in the nature of preliminary results. A discussion of previous studies concerning this issue emphasizes the need for obtaining more detailed information on sidestream smoke exposure and related variables.

Methods

All cases of primary cancer of the lung occurring in cases who reported never having smoked on a regular basis* were extracted from an ongoing case–control study of tobacco-related cancers conducted in a number of cities between 1971 and 1980† and described previously.[6] For each case, the hospital chart was re-examined in order to confirm the diagnosis and the absence of smoking

From the Division of Epidemiology, Mahoney Institute for Health Maintenance, American Health Foundation, 320 East 43rd Street, New York, New York.

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Address for reprints: Geoffrey C. Kabat, PhD, Division of Epidemiology, Mahoney Institute for Health Maintenance, American Health Foundation, 320 East 43rd Street, New York, NY 10017.

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* Our definition of a nonsmoker was someone who had never smoked as much as one cigarette, pipe, or cigar per day for a year.

† The majority of the cases (and matched controls) were interviewed at Memorial Hospital in New York City, 30 of the 37 male cases and 70 of the 97 female cases.

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throughout the patient's lifetime. The histologic type of lung cancer was obtained from the pathology report or the discharge summary for each case. Those cases in whom the diagnosis was not primary lung cancer or in whom there was an indication of smoking, even in the remote past, were excluded from the study. Those remaining in the study are referred to as "validated" nonsmokers.

A control was matched to each case on the basis of age (±5 years), sex, race (with 5 exceptions‡), hospital, date of interview (±2 years), and nonsmoking status. Controls were selected from a large pool of hospitalized patients who were interviewed over the same period as the cases and who had diseases which were not tobacco-related. The distribution of diagnoses among the controls was as follows: men, 62.1% other cancers, 24.3% benign neoplastic disease, 13.5% non-neoplastic disease; women, 59.9% other cancers, 14.4% benign neoplastic disease, 25.8% non-neoplastic disease.

All subjects were interviewed in the hospital with a standardized questionnaire including questions on demographic factors, occupation, occupational exposures, tobacco smoking, alcohol use, Quetelet's index ($kg/cm^2 \times 10{,}000$), and history of tobacco-related diseases. Two different versions of the questionnaire were used over the 10-year period, the first from 1971 to 1976, and the second from 1976 to 1980. Differences between the two questionnaires included a longer list of occupational exposures in the later version, and a longer list of previous diseases in the earlier questionnaire (diabetes, gout, bronchitis, emphysema, hypertension, asthma, pleurisy, pneumonia, bronchiectasis, and tuberculosis) than in the later version, which included only four questions on previous diseases (chronic bronchitis or emphysema, asthma, diabetes, and elevated blood pressure).

Alcohol consumption was assessed in current drinkers and exdrinkers (combined) relative to never-drinkers and occasional drinkers (combined). Occasional drinkers were those who consumed less than 1 ounce of whiskey equivalents of alcohol per day of beer, wine, and hard liquor combined. Alcohol intake was categorized into three levels: (1) never/occasional drinking, (2) 1 to 3.9 oz/day, and (3) 4+ oz/day.

In addition, a number of questions on exposure to passive smoking were introduced in an addendum to the main questionnaire in 1978, and the addendum was revised in 1979. Thus, information on passive smoking was obtained on only a subset of the subjects, for men, 25 of 37 cases and their matched controls; for women, 53 of 97 cases and their matched controls. This number of responses was obtained for those questions included in both versions of the addendum, whereas the number of responses was smaller for the question "Does your spouse smoke?", since this question appeared in only one version and since it was not answered by those subjects who were not married, widowed, separated, or divorced (see Table 3).

‡ One oriental male case was matched to a white control; two hispanic and two oriental female cases were matched to white controls.

TABLE 1. Histologic Type of Lung Cancer in Never Smokers and Smokers

	Men		Women	
	(No.)	(%)	(No.)	(%)
Never smokers				
Kreyberg type I	13	(35.1)	20	(20.6)
Epidermoid/squamous	13	(35.1)	16	(16.5)
Large cell/giant cell	0		4	(4.1)
Kreyberg type II	20	(54.1)	72	(74.2)
Adenocarcinoma	16	(43.2)	60	(61.9)
Alveolar	4	(10.8)	12	(12.4)
Mixed (Kreyberg I & II) and undifferentiated/ anaplastic	4	(10.8)	5	(5.2)
Total	37		97	
Smokers*				
Kreyberg type I	1187	(63.1)	341	(52.3)
Kreyberg type II	600	(31.9)	279	(42.8)
Mixed (Kreyberg I & II) and undifferentiated/ anaplastic	95	(5.0)	32	(4.9)
Total	1882		652	

* A more detailed breakdown by histologic type is not presented for smokers because this information was not coded. For the nonsmokers this information was retrieved manually.

Differences between cases and controls were assessed by the chi-square test for independence,[7] and by the Mantel-Haenszel extension test for linear trend.[8] Point estimates of the relative risk with test-based 95% confidence intervals were calculated following Miettinen's method.[9]

Results

For the 10-year period, 1971 to 1980, among 1919 cases of primary lung cancer in men, 37 (1.9%) occurred in validated nonsmokers. Among 749 lung cancer cases in women, 97 (13.0%) were validated nonsmokers. This difference in the proportion of nonsmokers in men and women is highly statistically significant, $\chi^2(1) = 137.21$, $P < 0.001$.

Histologic Type

Table 1 shows the histologic type of lung cancer for nonsmokers and smokers by sex. Among male smokers with lung cancer there were nearly twice as many Kreyberg type I§ cases as Kreyberg type II (1187 *versus* 600), while

§ Kreyberg type I includes squamous cell, oat cell, small cell and large cell carcinomas; Kreyberg type II includes adenocarcinoma, bronchiolar, and alveolar carcinoma.

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TABLE 2. Distribution of Background Variables in Cases and Controls

	Men				Women			
	Cases		Controls		Cases		Controls	
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)
Age								
≤49	13	(35)	12	(32)	12	(12)	15	(15)
50–59	11	(30)	12	(32)	26	(27)	24	(25)
60–69	7	(22)	10	(27)	29	(30)	34	(35)
70+	6	(14)	3	(8)	30	(31)	24	(25)
Total	37		37		97		97	
Religion								
Protestant	2	(6)	5	(14)	27	(28)	34	(36)
Catholic	16	(46)	14	(40)	31	(32)	36	(38)
Jewish	15	(43)	13	(37)	38	(40)	24	(25)
Other	2	(6)	3	(9)	0	(0)	1	(1)
Total	35		35		96		96	
Yr of education								
1–11	3	(5.4)	6	(16.2)	38	(39.2)	29	(29.9)
12	7	(16.2)	11	(29.7)	25	(27.8)	37	(38.1)
13–15	6	(21.6)	8	(21.6)	14	(15.5)	15	(15.5)
16+	20	(56.8)	12	(32.4)	16	(17.5)	15	(15.5)
Total	37		37		97		97	
Occupational status								
Professional	22	(59.5)	14	(37.8)	8	(8.2)	11	(11.3)
Skilled	6	(16.2)	7	(18.9)	26	(26.8)	35	(36.1)
Semiskilled	2	(5.4)	9	(24.3)	6	(6.2)	6	(6.2)
Unskilled	3	(8.1)	2	(5.4)	8	(8.3)	5	(5.2)
Housewife	0	—	0	—	38	(39.2)	28	(28.9)
Retired/unemployed	4	(5.5)	5	(13.5)	11	(11.3)	12	(12.4)
Total	37		37		97		97	

among female smokers the numbers were more similar (341 *versus* 279). This difference is statistically significant, $\chi^2(1) = 25.91$, $P < 0.001$. Among male never-smokers, there were 13 Kreyberg type I *versus* 20 Kreyberg type II cases, while among females, there were 20 Kreyberg type I *versus* 72 Kreyberg type II cases. Although the number of male nonsmoking cases is small, the difference between men and women is statistically significant, $\chi^2(1) = 3.90$, $P < 0.05$. Furthermore, the difference between the proportions of Kreyberg I and Kreyberg II in never-smokers compared with smokers is statistically significant in both sexes (for men, $\chi^2(1) = 10.54$, $P < 0.005$; for women, $\chi^2(1) = 35.46$, $P < 0.001$).

Age

Table 2 gives the age distribution of cases. Male cases are significantly younger than female cases ($\chi^2(3) = 11.30$, $P < 0.025$). The mean age for men was 53.9 years (SD [standard deviation] 14.3) compared with 61.6 (SD 11.3) for women. This younger age of male cases appears to hold for both Kreyberg I and Kreyberg II types: the mean age for Kreyberg I and Kreyberg II lung cancer in men was 52.8 and 53.6 years, respectively, while in women Kreyberg I had a mean age of 63.7, and Kreyberg II had a mean of 61.0 years.

Education

Kreyberg II cases appeared to be more educated than Kreyberg I cases in both sexes (data not presented).

Case-Control Comparisons

There were no differences in male cases and controls by religion, proportion of foreign born, marital status, and residence in childhood, adolescence, and adulthood. Male cases were better educated (57% of cases had gone beyond college compared to 32% of controls), and a higher proportion were professionals (60% of cases compared to 38% of controls) (Table 2). These differences did not reach statistical significance.

Female cases and controls did not differ significantly on proportion of foreign born, marital status, education, occupational status, or residence in childhood, adolescence, or adulthood. There was a nonsignificantly higher proportion of Jewish women among cases compared to their controls (40% *versus* 25%) (Table 2). In both cases and controls, the proportion of urban dwellers increased from 70% in childhood to 80% in adulthood.

History of previous diseases: No case-control differences were found for history of chronic bronchitis, emphysema, diabetes, asthma, pneumonia, or hypertension in males. In females, there were similar findings, except more female cases had a previous history of pneumonia than controls: 16/40 cases *versus* 3/38 controls ($\chi^2(1) = 10.9$, $P = 0.001$).

Quetelet's index: Quetelet's index was calculated using the subject's weight 5 years prior to diagnosis for 22 male cases and their matched controls and for 50 female cases and controls on whom this information was available. No difference was seen between cases and controls of either sex.

Alcohol: No significant differences in alcohol intake were found between cases and controls of either sex.

Occupational exposure: No differences in occupational exposures were observed between male cases and controls. In females, the only significant difference was that 14 cases reported working in a textile-related job compared to 5 controls (relative risk, 3.10; 95% confidence interval 1.11–8.64). Of the 14 female cases, 2 were diagnosed with Kreyberg I, 11 with Kreyberg II and 1 had mixed-type lung cancer. For those cases and controls interviewed between 1976 and 1980, information on the duration of exposure to occupational and environmental substances was available. There was no difference in the mean num-

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ber of years of exposure in textile-related jobs (16 years) of cases and controls. Among the cases, the specific occupations were the following: one seamstress, two dressmakers, one sewing-machine operator, one assembler and yarnwinder, one dress-shop worker, two salesladies who had done factory work, one apparel manufacturer, one clothing packer, one typist, one washerette/housekeeper, one bookkeeper, and one housewife.

Among the 37 male cases only a few (5) reported exposures to substances of potentially etiologic interest. An electronics engineer had 35 years of exposure to cleaning chemicals; a designer had 25 years of exposure to chemicals and acids and 15 years of exposure to plastics and glues; a director of sales for a chemical corporation (a chemist) had 12 years of exposure to chemicals and acids; an upholsterer had 30 years of exposure to asbestos, rubber, and solvents; and a machine shop attendant had 37 years of exposure to metals, grease, and oil.

Among the 97 female cases, in addition to exposure to textile work reported by 14, few reported other exposures. The assembler/yarnwinder who reported exposure to textiles also reported exposure to metals for 28 years; a machine operator had 10 years of exposure to metals; an assistant medical technician had 10 years of exposure to chemicals and acids; a social worker had 5 years of exposure to metals and welding; an electronic prototype technician had 14 years of exposure to chemicals and acids, metals and solvents; and a chambermaid had 23 years of exposure to ammonia.

We looked separately at the small number of cases who developed lung cancer younger than age 40, eight men and six women. The occupations of the men included an accounting professor, an accounting clerk (who had been a teacher for 11 years), a neurosurgeon, a stock trader, a postal service clerk, a law student, a salesman, and a self-employed president of a supply company. None of the men reported any exposures. The female cases included two housewives, an assistant manager for the American Automobile Association, an electronic prototype engineer (mentioned above), a telephone operator, and a high school teacher. Only the electronic prototype engineer reported any exposures. The distribution of histologic types among these younger cases did not appear to differ from that of all nonsmoking cases.

Passive inhalation: Of the 25 male cases and controls who were asked about exposure to other people's cigarette smoke at home, six male cases reported having been exposed compared to 5 controls (Table 3). Eighteen of 25 cases reported having been exposed to cigarette smoke at work compared to 11 of 25 controls. The difference is just statistically significant ($P = 0.05$). Mantel extension test for linear trend in the frequency of exposure (four levels) in cases and controls gives a chi-square of 2.88, $P < 0.005$. The number of male cases and controls who reported that their wives smoked was identical, 5 of 12 in both groups. In both groups the wives had smoked for comparable periods of time.

TABLE 3. Exposure to Passive Inhalation Among a Subset of Cases and Controls

	Men				Women			
	Cases		Controls		Cases		Controls	
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)
At home*								
Yes	6		5		16		17	
No	19		20		37		36	
Total	25		25		53		53	
At work†								
Yes	18		11		26		31	
No	7		14		27		22	
Total	25		25 ($P < 0.045$)		53		53	
Spouse smoke‡								
Ever	5		5		13		15	
Never	7		7		11		10	
Total	12		12		24		25	

* Current exposure on a regular basis to family members who smoke.
† Current exposure on a regular basis to tobacco smoke at work.
‡ Spouse's current or past smoking habits.

No differences on exposure to passive smoking at home or at work were found in women, 16 of 53 cases were exposed at home compared to 17 of 53 controls, and 26 of 53 cases were exposed at work compared to 31 of 53 controls. Of the women who were asked about their spouses' smoking habits, no differences between cases and controls were found in the proportion who smoked, 13/24 for cases *versus* 15/25 for controls. Again, years of smoking in the cases' husbands did not differ from years of smoking in the controls' husbands.

Discussion

Due to the powerful role of smoking in the etiology of lung cancer, other risk factors can best be studied in nonsmokers with confirmed nonsmoking histories. Thus, a key feature of this investigation is that in order to "validate" the diagnosis of primary lung cancer (obtained from the discharge summary or the pathology report) and the nonsmoking status of all study subjects (obtained in the original interview), we went back to the hospital records and abstracted information on diagnosis and smoking history. If the chart indicated that the patient had smoked tobacco at any period of his or her life, the person was excluded from the study. In the rare instance that no mention of smoking history was found in the chart, the patient was included. Of the 156 cases of lung cancer in

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our computer file of self-reported never-smokers, review of the hospital chart revealed that 13 were actually smokers or had smoked at some time, and 9 were not primary lung cancers. These 22 cases were excluded from the analysis. Confirmation of the diagnosis and nonsmoker status of the controls was carried out in the same way as for the cases. For none of the controls was the self-reported nonsmoking status contradicted by information in the chart.

The finding that more cases gave a conflicting response on whether or not they had ever smoked than controls (13 of 147 primary lung cancer cases compared to none of 134 controls) is of significance. This suggests that some lung cancer cases tend to deny a smoking history more than controls with non-tobacco-related diseases. In a study of the role of cigarette smoking in lung cancer, such denial of cigarette consumption or under-reporting, which may also take place, would tend to reduce the estimate of the relative risk. In a study of lung cancer in nonsmokers, the inclusion of cases with a smoking history (misclassification) would also reduce associations of the disease with other risk factors.

Although we attempted to eliminate all smokers from among the cases and controls by using a conservative definition of nonsmoker and by excluding any subject with a history of smoking either in the questionnaire or in the hospital chart, it is possible that some subjects who reported never having smoked actually did smoke at some time.

The current study confirms earlier findings that among lifelong nonsmokers lung cancer is exceedingly rare, and that the more conservative the definition of nonsmoker and the more detailed the smoking history, the lower is the proportion of nonsmokers found among lung cancer cases.[3]

Histologic Type

As found in earlier studies, Kreyberg type II (primarily adenocarcinoma) is more common in nonsmokers with lung cancer than in smokers and, in both groups, Kreyberg type II is more common in women. The percentages of nonsmoking cases with adenocarcinoma in our study (43% of males, 62% of females) are in close agreement with those from the American Cancer Society's prospective study (46% of males, 59% of females, L. Garfinkel, personal communication, 1982). In view of the differences in design and method of selection of subjects, this agreement suggests that these percentages may be representative of nonsmoking lung cancer cases generally.

Sex Ratio

In our nonsmoking cases there are 2.6 times as many females as males, even though the male–female incidence ratio for lung cancer is 2.4,[10] and the male–female ratio among all lung cancer cases in our file is 2.6 (1919/749). The larger number of nonsmoking women with lung cancer compared with nonsmoking men is presumably due to the historically higher proportion of nonsmokers among women compared to men. Doll found no difference in the age-specific death rate from lung cancer among nonsmoking males and females.[1] Similarly, Garfinkel[11] found no difference in the age-adjusted lung cancer mortality rate for nonsmoking men and women.

Case-Control Comparisons

Previous diseases: Our finding that female cases had a higher frequency of previous history of pneumonia compared to controls is difficult to interpret since we do not have information on the age at diagnosis or on the duration of pneumonia.

Occupation: Earlier case studies of lung cancer in nonsmokers have included occupations in males with exposure to dust and/or fumes, *i.e.*, a carpenter, a joiner, a fitter, and a flour miller among the 7 male cases in Doll's study;[1] two painters, a smelter, a blacksmith, a gasoline truck driver, a gasoline and oil delivery man and gas station attendant, a cabinet maker, a sawmill worker, and an engineer among 20 male cases in Wynder's study;[2] a plumber/steamfitter and an auto body and fender repairman among 8 male cases in the study by Wynder and Berg.[3] Among female cases, the occupations were less suggestive of exposure to inhaled substances. These studies interviewed small numbers of nonsmoking cases, and did not make use of a comparison group.

Our findings of a statistically significant threefold excess risk of lung cancer among women who reported having worked in the textile industry is of interest. Doll, in his study of lung cancer among nonsmokers, lists occupations of more than 3 years duration in 7 male and 40 female lung cancer cases. Out of 31 women who had been employed outside the home, 5 had worked as seamstresses or dressmakers.[1]

However, there is no clear relationship in our data between duration of exposure and risk of disease. The mean number of years of exposure was the same for cases and controls. Most importantly, it is not clear that there is a single exposure or group of exposures that all of the workers in textile-related jobs have in common.

Furthermore, it should be emphasized that our occupational data are limited since there was room only to code one occupation—that of longest duration—and two exposures. Occupational and environmental exposures to specific substances were obtained by asking the subjects whether they had ever been exposed for more than a year to any of a list of substances. Self-reported exposures of this kind are subject to information bias since awareness of such exposure could be expected to vary with the in-

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dividual, with educational level, with different jobs, and between cases and controls. In only 7 of the 14 cases did the coded occupation mention textile work. The remaining seven cases reported occupations not specifically associated with textiles, such as "typist," but reported exposure to textiles. Evidence from existing occupational studies of lung cancer risk in textile workers is scant.[12-14] No cohort study of textile workers appears to have been carried out.

The apparently minor role of occupational exposures in our male cases is consistent with the high percentage of professionals (60%) among them. Although our data do not suggest an important role of occupation or exposure to specific substances, it would be desirable in the future to obtain more detailed and objective occupational histories on cases of lung cancer occurring in nonsmokers.

Passive inhalation: The plausibility of a role of passive inhalation in lung cancer can be questioned on several grounds. Although sidestream cigarette smoke contains higher concentrations of toxic components than mainstream smoke,[15] it is diluted in the ambient air to varying degrees (depending on the size and shape of the room, proximity to the smoker, and ventilation) by the time it reaches the passively exposed person. As shown by Auerbach and coworkers,[16] the changes in the bronchial epithelium characteristic of smokers are rarely observed in lifetime nonsmokers.

Nevertheless, the possibility that heavy exposure to secondhand smoke over a long period of time could lead to increased cancer risk cannot be ruled out at present. Because questions on passive inhalation were introduced in our questionnaire in 1978, we only have information on this factor for between 28% and 68% of our subjects depending on the specific question. We present the distributions of responses to these questions as preliminary data since the numbers are small. Cases do not differ from controls except for the greater exposure to cigarette smoke at work reported by male cases compared to male controls. Those cases who reported passive inhalation exposure did not differ in their distribution of histologic types from unexposed cases. The difference between exposure to cigarette smoke at work between male cases and controls could be due to information bias, although there is no indication of such bias in the responses to the other questions on passive inhalation.

The studies which, to date, have addressed the issue of passive inhalation and lung cancer have differed in methodology, the population studied, the type of lung cancer studied, the degree of histologic confirmation, and in results. These studies are summarized in Table 4. They have been commented on by a number of investigators.[11,17-19] We wish to draw attention here to several points which are crucial in assessing a contribution of passive smoking to lung cancer and which need to be considered in future studies. First, the proportion of histologically confirmed diagnoses in the studies listed in Table 4 ranged from 35% (Trichopoulos *et al.* [20]) to 82% (Chan and Fung [21]). Given the difficulty of diagnosing lung cancer, histologic confirmation is essential. Second, Trichopoulos *et al.*[20] excluded adenocarcinoma and terminal bronchiolar cases, whereas adenocarcinoma predominated in Hirayama's cases[22] (personal communication, 1981), in those of Chan and Fung,[21] and in our cases. In the American Cancer Society study reported by Garfinkel,[11] histologic type was obtained for lung cancer cases during the first 6 of 12 years of the study. Seventy percent of these cases had histologic confirmation but some of these were only identified as "carcinoma." Among the cases with confirmed histology and information on specific cell type, 46% of the male and 59% of female nonsmokers had adenocarcinoma compared to 23% among male and 46% among female smokers (personal communication). Since little is known about the etiologic significance of different histologic types and since the distribution of types differs in different populations, it is premature to restrict studies of passive inhalation to particular types.

Third, although histologic classification of lung cancer is imperfect, it is desirable to stratify by the major histologic types in the analysis if the number of cases permits since different histologic types may have different etiologies.

Finally, all of the previous studies used the amount and duration of spouse's smoking as the measure of exposure to passive inhalation. Focus on the spouse's smoking may fail to provide an adequate measure of the subject's exposure for a number of reasons: (1) a subject's actual exposure depends on how much time the smoking spouse smokes in his or her immediate presence; the spouse could be a heavy smoker but spend very little time at home; (2) in addition to the current spouse's smoking habits, those of former spouses may be equally important; (3) the subject may live with other relatives who smoke; (4) exposure to tobacco smoke at work can be a substantial proportion of a person's exposure; (5) exposure in cars, commuter trains, buses, and in other situations, such as restaurants, movie theaters, etc., could be significant. It is for these reasons that we have recently revised our questionnaire to include detailed questions which will give a more complete picture of the subject's exposure, both in respect to different environmental settings and to duration of exposure for each specific component.

If passive inhalation in nonsmokers is associated with increased lung cancer risk, by what mechanism does it exert its effect? Since adenocarcinoma is the most common histologic type of lung cancer in nonsmokers, one could hypothesize that inhaled sidestream smoke increases

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TABLE 4. Summary of Studies of the Role of Passive Inhalation in Lung Cancer in NonSmokers

Author/ type of study/ population	No. of cases	Histology	Findings	Comments
Hirayama (1981)[22] Prospective/ Japanese nonsmoking wives aged 40+ years	174 deaths in married nonsmoking women w/lung ca among 91,540 nonsmoking married women	Out of a sample of 23 cases, 17 were adenocarcinoma	A dose-response relationship was seen between the nonsmoking wives' risk and the husbands' smoking habit: wives of exsmokers or of 1–19 cigs/day-smokers had RR = 1.61; wives of smokers of ≥20 cigs/day had RR = 2.08	Exposure index was based on smoking habits of husbands
Garfinkel (1981)[11] Analysis of data from two prospective studies/ACS population and Dorn study of veterans[11]	195 deaths from lung ca among male nonsmokers; 564 deaths from lung ca among female nonsmokers (ACS); 168 lung ca deaths among nonsmokers (Dorn)	Histologic confirmation of dx in 69% of cases in first 6 years of ACS study. Among lung cancer cases with confirmed detailed histology, 46% of male and 59% of female nonsmokers had adenocarcinoma compared with 23% of male and 46% of female smokers (personal communication)	No significant increase in lung ca risk seen in nonsmoking wives of smoking husbands compared with nonsmoking wives of nonsmoking husbands	Exposure index was based on smoking habits of husbands
Trichopoulos *et al.* (1981)[20] Case-control/white female residents of Athens, Greece	40 female nonsmokers w/lung ca other than adenoca or terminal bronchiolar	14 cases were histologically confirmed; 19 were cytologically confirmed; 18 were clinically confirmed; excluded adenocarcinoma and terminal bronchiolar	RR of lung ca associated w/ having a husband who smokes <1 pack/day was 2.4; RR associated w/ having a husband who smokes >1 pack/day was 3.4. (χ^2 for linear trend = 6.45; $P < 0.02$)	Exposure index was based on smoking habits of husbands and former husbands
Chan and Fung[21] Case-control/ Hong Kong Chinese	Only two nonsmokers out of 208 male lung ca cases; 84 nonsmokers out of 189 female lung ca patients	15 of the 84 female cases were squamous or epidermoid ca; 38 were adenocarcinoma; 15 had no histologic verification	Among nonsmoking women the proportion of cases whose spouse smoked was slightly lower than that of controls (34 of 84 or 40.5% *vs* 66 of 139 or 47.5%). Among nonsmoking women, there was no significant difference in the proportion of cases who used kerosene fuel in cooking compared with controls.	It is unclear what question was used regarding inhalation since in an earlier paper*, the question is given as "Are you exposed to the tobacco smoke of others at home or at work?"; whereas here reference is made only to "smoking habits of spouses." No information is given on how many subjects were married

Ca: cancer; dx: diagnosis; cigs: cigarettes; RR: relative risk; *vs*: *versus*.
* Chan WC, Colbourne MJ, Fung SC, Ho HC. Bronchial cancer in Hong Kong 1976–1977. *Br J Cancer* 1979; 39:182–192.

the risk for this type. Volatile components of cigarette smoke, including volatile nitrosamines, are more likely than respirable particulate matter to reach the periphery of the lung. Current findings suggest most lesions in nonsmokers are located in the deeper portions of the lung. Nonsmokers exposed to cigarette smoke in enclosed spaces are reported to have increased levels of carbon monoxide in their blood,[23–25] which suggests that other volatile components could reach the lung. It would be important to know in this regard whether the location of lesions in the lungs of nonsmoking lung cancer cases with exposure to passive inhalation differs from that among smokers.

In addition to the etiologic factors discussed in this article, other possible explanations of the occurrence of lung cancer in nonsmokers should also be considered.

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Exposure to ionizing radiation in the course of radiation treatment could be responsible for some cases. Also, Auerbach and coworkers[26] have suggested that lung cancer could arise in nonsmokers secondary to healed tuberculosis scars, although this is unlikely to account for many cases.[27] Another possibility is that lung cancer in nonsmokers, especially adenocarcinoma, is estrogen-related since it is more common in women than in men. It has been shown that adenocarcinoma of the lung frequently contains estrogen receptors.[28] Still another possibility is that carcinogens of nutritional origin could be carried to the lung by the blood. These possibilities deserve epidemiologic exploration.

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Garfinkel, L., Auerbach, O. and Joubert, L., "Involuntary Smoking and Lung Cancer: A Case-Control Study," Journal of the National Cancer Institute 75(3): 463-469, 1985.

This case-control study, conducted in New Jersey and Ohio, included 134 cases and 402 age- and hospital-matched controls. Lung cancer cases were ascertained using hospital records and cancer registries. Controls had been diagnosed with colon-rectum cancer. All cases were histologically confirmed. Some proxy interviews were conducted, usually with spouse or children. One table shows the variation in ORs related to respondent type; for instance, based on questions about husband's smoking habit, an OR when the case responded was 0.83; when the husband, 0.77; and when the case's child, 3.57. Exposure questions were asked regarding husband's smoking, smoking by others in the home, smoking in the workplace and smoking by others during childhood.

ORs were calculated for four methods of classifying smoke exposure: "exposed to smoke over last 5 year," OR = 1.28 (95% CI 0.96-1.70); "exposed to smoke over last 25 year," OR = 1.13 (95% CI 0.60-2.14); "husband smoked," OR = 1.22 (95% CI 0.97-1.71); and "husband smoked at home," OR = 1.31 (95% CI 0.94-1.83). Additionally, for women whose husbands smoked ≥40 cigarettes/day, an OR of 1.99 (95% CI 1.13-3.50) was calculated. For those whose husbands smoked ≥20 cigarettes/day, the reported OR was 2.11 (95% CI 1.13-3.95). For exposure in the workplace, ORs less than 1.0 were reported. Exposure during childhood was associated with a statistically nonsignificant OR of 0.91.

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Involuntary Smoking and Lung Cancer: A Case-Control Study[1]

Lawrence Garfinkel,[2] Oscar Auerbach,[3] *and* Lou Joubert[2,4]

ABSTRACT—In a case-control study in 4 hospitals from 1971 to 1981, 134 cases of lung cancer and 402 cases of colon-rectum cancer (the controls) were identified in nonsmoking women. All cases and controls were confirmed by histologic review of slides, and nonsmoking status and exposures were verified by interview. Odds ratios (OR) increased with increasing number of cigarettes smoked by the husband, particularly for cigarettes smoked at home. The OR for women whose husbands smoked 20 or more cigarettes at home was 2.11 (95% confidence limits: 1.13, 3.95). A logistic regression analysis showed a significant positive trend of increasing risk with increased exposure to the husband's smoking at home, controlled for age, hospital, socioeconomic class, and year of diagnosis. Comparison of women classified by number of hours exposed a day to smoke in the last 5 years and in the last 25 years showed no increase in risk of lung cancer.—JNCI 1985; 75:463-469

Much interest has been expressed in the past several years in the reported relationship of involuntary or passive smoking and the development of lung cancer. Hirayama (*1*), in a prospective study in Japan, reported a 2:1 RR for nonsmoking women married to smokers as compared to the RR for nonsmokers married to nonsmokers. Trichopoulous et al. (*2*), in a study in Greece, found that nonsmoking women with husbands who smoked had an OR about 2.5 times as high as that of women with husbands who never smoked, and the OR rose to 3.4 in women whose husbands smoked more than one pack of cigarettes a day. In another case-control study, Correa et al. (*3*) found nonsmoking women married to smokers with a lifetime consumption of 41 or more pack years had an OR 3.5 times as high as the OR of women married to nonsmokers.

In an analysis of data from the American Cancer Society's prospective study, Garfinkel (*4*) found little if any increase in RR of lung cancer for nonsmoking women married to smokers (*4*). The RR was 1.34 for light smokers and 1.10 for those whose husbands smoked 20 or more cigarettes a day. Kabat and Wynder (*5*) in a pilot study found no extra lung cancer risk in women and in nonsmoking men exposed to smoke at home, but nonsmoking men exposed at work showed a slight increase in risk. Kabat and Wynder measured exposure both by the spouse's smoking habit and the subject's report of direct exposure.

An investigation by Sandler et al. (*6*) of relatively young cancer cases in North Carolina found an overall 1.6 OR (smokers and nonsmokers) for exposed vs. nonexposed cancer cases. Exposed cases were those in which the husband smoked. Exposed nonsmokers had a higher OR than that of exposed smokers. In nonsmokers the OR were elevated and statistically significant for cancers of the cervix, breast, and endocrine glands. Occurrence of cancer in the latter two sites previously had not been associated with cigarette smoking. Lung cancer also showed an elevated OR but was not statistically significant; however, the number of cases was small.

Two papers in Hong Kong by Chan and Fung (*7*) and by Koo et al. (*8*) show very little difference between cases and controls with respect to involuntary smoking and lung cancer.

Except for the two prospective studies, all of these studies were based on relatively few lung cancer cases in female nonsmokers; the number of cases ranged from 22 to 77 in various case-control studies.

In a previous paper, we pointed out that in any study of involuntary smoking and lung cancer, categorizing nonsmokers by the smoking habit of the spouse may lead to error in classification of exposure. In the United States particularly, there may be many women, married to nonsmokers, who are exposed to the smoke of others at work or in other areas. Conversely, some individuals married to smokers may suffer acute effects from inhaling smoke and consciously avoid such exposure. A survey of 38,000 subjects by Friedman et al. (*9*) confirmed this hypothesis. About 40% of women nonsmokers and 50% of men nonsmokers who were married to nonsmokers were exposed to the smoke of others for some periods of time during a week, and 47% of nonsmoking women married to smokers reported that they were not exposed to tobacco smoke at home. In the study reported here, we record the smoking habit of husbands (total No. of cigarettes smoked and No. smoked at home), as well as the number of hours a day the subjects were exposed to the smoke of others at home, at work, and in other areas.

Other causes for concern are establishment of the microscopic diagnosis of primary lung cancer and

Abbreviations used: CL=confidence limits; OR=odds ratio(s); RR=relative risk(s).

[1] Received April 22, 1985; accepted June 20, 1985.

[2] Department of Epidemiology and Statistics, American Cancer Society, 4 West 35 St., New York, NY 10001.

[3] Veterans Administration Medical Center, East Orange, NJ, and University of Medicine and Dentistry of New Jersey, Newark, NJ.

[4] We thank Dr. Robert V. P. Hutter, St. Barnabas Hospital, Livingston, NJ; Dr. Herbert Derman, Riverside Methodist Hospital, Columbus, OH; Dr. Jerry Rothenberg, Morristown Memorial Hospital, Morristown, NJ; and Dr. Douglas Smith, Middlesex General University Hospital, New Brunswick, NJ, for granting us access to medical records and pathologic material. We also thank the following individuals for making valuable suggestions regarding the manuscript: Mr. William Haenszel, Dr. E. Cuyler Hammond, Dr. Geoffrey Howe, Mr. Edward Lew, Mr. Herbert Seidman, and Dr. Steven Stellman. We also thank Ms. Nancy La Verda and Mr. Henry Vasquez for assistance in processing the data.

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verification of the smoking history. In a study of the histologic type of lung cancer in relation to asbestos exposure, 49 of 774 men and women with a discharge diagnosis of microscopically proved lung cancer were recorded as nonsmokers in the hospital chart (*10*). After review of hospital records, histologic sections, and interviews, only 10 cases remained who had died of primary lung cancer and who had never smoked. One-half of the others had smoked at some time and, one-half the confirmed nonsmokers had a primary cancer other than that of the lung.

It is apparent, therefore, that more studies on involuntary smoking are needed, with particular attention given to obtaining microscopic proof of primary lung cancer and more detailed information about exposures to cigarette smoke.

METHODS

To have available enough subjects for a case-control study of involuntary smoking, we obtained access to the records of 4 hospitals—3 in New Jersey and 1 in Ohio. In each of these institutions, we identified all lung cancer cases in women recorded during 1971-81. In 2 hospitals the cases were selected from the Tumor Registry; in 1 hospital, they were selected from the surgical index in the pathology department; and in the other hospitals, records from the pathology laboratory were checked against the medical records diagnostic discharge index. No case was selected that had been diagnosed prior to 1971. Cases with cancer of the colon-rectum served as controls. Colon-rectum cancers have been shown in epidemiologic studies not to be related to cigarette smoking. Charts then were located and reviewed. Cases that were diagnosed clinically only or by cytology, or as sarcoma or lymphoma of the lung, were excluded. Those that occurred in smokers (or ex-smokers), according to hospital records, also were set aside. Only those charts in which the patient was specified as a nonsmoker, or in which the smoking habit was not recorded, were further investigated.

All the slides for these cases and controls were pulled from the files (an average of ≈15 slides/case) and were reviewed blind (by O. A.). In a small sample, slides for cases and controls were reviewed a second time to check consistency of the findings. Another sample of slides for smokers with lung cancer, and for subjects with diagnoses of sites other than lung or colon-rectum, also were selected for histologic review and were mixed in with the slides of nonsmokers. If slides were missing or not available, or of too poor quality for accurate diagnosis, the blocks for the case were located and new slides were prepared.

An interview based on a standard questionnaire was obtained for all cases and controls, along with microscopic proof. The interview was with the woman if she were still alive or with next of kin if she had died. Seven interviewers did all the questioning; three did interviewing in all 4 hospitals. About three-quarters of the interviews were with the patient or with spouse or children. All other informants had known the subject for at least 25 years and were able to supply the necessary information. All interviews were reviewed by the supervisor. When the information was incomplete, another respondent was contacted. A second interview was obtained in about 10% of the cases and controls.

Women who had never married and who lived with another member of the family were classified according to their relative's smoking habits. Therefore, the word "husband" as used in this paper means husband or cohabitant living in the same household. Of the cases, 57% were married and living with their husbands at the time of the cancer diagnosis. The interview included questions on current smoking habits of the husbands of the cases and controls up to the present time or to the time of death; on the number of cigarettes smoked per day at home, and the number of years they had smoked. The interviewer also asked about the average number of hours a day the woman had been exposed to the smoke of others at any time during the past 5 years, during the past 25 years at home, while at work and in other areas, and during her childhood. Women whose husbands smoked cigarettes only occasionally were counted as not exposed; occasional exposure at home, work, or in other areas also was counted as not exposed.

We matched 1 lung cancer case to 3 colon-rectum cancer cases. Controls were matched to within 5 years of age and were from the same hospital. In most age groups there were many colon-rectum cancers in women of the same ages for matching purposes. The colon-rectum cases were checked for histologic proof in the same way as were the lung cancer cases, and the smoking interviews were obtained by the same interviewers who obtained the lung cancer interviews. The interviewers were not told the diagnoses, nor did they know the hypothesis of the study.

Several different analytic procedures were used: The Mantel-Haenszel procedure for obtaining a point estimate of the OR with a 1:3 match was employed, as adapted by Pike and Morrow (*11*), with CL as shown by Miettinen (*12*). To compare subgroups of exposures, the matching was broken, and OR and CL were computed by the Mantel-Haenszel method. In addition, a logistic regression model was used, with estimation and testing procedures as given by Breslow and Day (*13*).

To permit comparison with previous studies, the subjects' exposures to cigarette smoke were classified in several different ways: 1) exposure over the last 5 years, 2) exposure over the last 25 years, 3) exposure to cigarettes smoked by husband, and 4) exposure to cigarettes smoked by husband at home.

RESULTS

Table 1 shows the process through which data for 134 cases of lung cancer in nonsmoking women were obtained from the four hospitals. Of 1,175 women listed as having lung cancer, 892 (76%) were smokers or had smoked in the past, according to hospital records. Of the 283 remaining women, 36 (12.7%) were proved histologically to have other than lung cancer upon

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TABLE 1.—*Lung cancer in women who never smoked. Records of 4 hospitals, 1971–81*

Status	No. of women examined					
	At hospitals:				Total	%
	A	B	C	D		
Microscopic proof of lung cancer on hospital record	243	93	276	563	1,175	
Smoker	200	70	182	440	892	
Nonsmoker or smoking habits not stated[a]	43	23	94	123	283	100.0
Reinterview revealed smoker	15	3	41	54	113	39.9
Reinterview revealed nonsmoker	18	14	45	57	134	47.3
No microscopic proof of lung cancer	10	6	8	12	36	12.7

[a] 68% of the hospital records listed patient as nonsmoker; in 32% of the records, smoking habits were not stated.

review of slides by one of us (O. A.), and 113 (39.9%) were found to be smokers upon reinterview. Only 134 (47.3%) were lifetime nonsmokers with histologically proved primary lung cancer. They were the only cases therefore suitable for this study. Among the colon-rectum cases, there were many fewer that were misdiagnosed—only 1.4%.

The age distribution of the cases and controls is shown in table 2. More than half were 70 years of age or older, and 22% were 80 years of age or older at the time of diagnosis. The histologic diagnosis of lung cancer cases was as follows: 65% adenocarcinoma, 16% large cell, 8% squamous cell, 4% oat cell, 3% alveolar cell, 3% mixed, and 1% too undifferentiated for classification by cell type.

Table 3 shows the OR and CL for risk of lung cancer, according to the 4 methods of classifying smoke exposure. The OR ranged from 1.13 to 1.31. All 4 methods resulted in lower 95% CL of less than 1 and were not statistically significant.

Table 4 shows the average number of hours per day that cases and controls were exposed to other people's

TABLE 2.—*Age distribution of lung cancer cases and controls*

Age, yr	Cases		Controls	
	No.	%	No.	%
40–49	5	3.7	17	4.2
50–59	28	20.9	86	21.4
60–69	28	20.9	88	21.9
70–79	44	32.9	121	30.1
80–89	24	17.9	82	20.4
≥90	5	3.7	8	2.0
Total	134	100.0	402	100.0

TABLE 3.—*OR for matched groups of women for risk of lung cancer from exposure to smoke, as classified in 4 categories*

Classification	Risk of lung cancer for women	
	OR	CL
Exposed to smoke over last 5 yr	1.28	0.96–1.70
Exposed to smoke over last 25 yr	1.13	0.60–2.14
Husband smoked	1.22	0.97–1.71
Husband smoked at home	1.31	0.94–1.83

smoke for the last 5 years and for the last 25 years. The women exposed during the last 5 years had an OR (adjusted for hr exposed per day) of 1.28 (95% CL: 0.98, 1.66) and those exposed for the last 25 years had an OR of 1.12 (CL: 0.81, 1.42). No increasing trend with increasing exposure was apparent in either group. In the 5-year exposure group, the OR went down with increased exposure, but the OR in each of the exposure groups was not statistically significant.

Table 5 and text-figures 1 and 2 show exposure classified by the husband's smoking habits. The OR for women married to smokers was 1.23 (CL: 0.94, 1.60); for those whose husband smoked at home it was 1.31 (CL: 0.99, 1.73). Women whose husbands smoked 40 or more cigarettes a day had an OR of 1.99 (CL: 1.15, 3.50). Women whose husbands smoked 20 or more cigarettes at home had an OR of 2.11 (CL: 1.13, 3.95). These were the only specific smoking groups in which the OR were statistically significant. The Mantel extension test for

TABLE 4.—*Number of cases and controls exposed to smoke of others during 5 and 25 yr before diagnosis*

Variable	Exposure, No. of hr/day					Total No. of women
	None	1–2	3–6	≥7	Total	
Last 5 yr						
No. of cases	80	15	25	14	54	134
No. of controls	263	31	59	49	139	402
OR	1.00	1.59	1.39	0.94	1.28	
95% CL		0.90–2.72	0.96–2.03	0.69–1.28	0.98–1.66	
Last 25 yr						
No. of cases	42	17	45	30	92	134
No. of controls	136	72	109	85	266	402
OR	1.00	0.77	1.34	1.14	1.12	
95% CL		0.60–0.99	0.96–1.87	0.83–1.57	0.81–1.42	

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TABLE 5.—*Smoke exposure before lung cancer diagnosis, as classified by husband's smoking habits*

Variable	Husband's total smoking habits						
	None[a]	Cigarettes/day			Cigar and/or pipe	All types of smoking	Total No. of women
		<20	20–39	≥40			
No. of cases	43	11	32	30	18	91	134
No. of controls	148	45	102	52	55	254	402
OR[b]	1.00	0.84	1.08	1.99	1.13	1.23	
95% CL		0.61–1.16	0.81–1.44	1.13–3.50	0.78–1.62	0.94–1.60	
	Husband's smoking habits at home						
	None[a]	Cigarettes/day			Cigar and/or pipe	All types of smoking	Total No. of women
		<10	10–19	≥20			
No. of cases	44	29	17	26	18	90	134
No. of controls	157	90	56	44	55	245	402
OR[c]	1.00	1.15	1.08	2.11	1.17	1.31	
95% CL		0.84–1.58	0.76–1.54	1.13–3.95	0.80–1.70	0.99–1.73	

[a] Figures include single women living alone. Cohabitants living with single women were classified as "husbands."
[b] Mantel extension test for trend (one tailed): $\chi = 2.31$, $P<.025$.
[c] Mantel extension test for trend (one tailed): $\chi = 2.35$, $P<.025$.

trend in both groups was statistically significant ($P<.025$, one-tailed test).

Analysis also was done for years of smoking. There were statistically significant OR for those smoking for 20–29 years (2.25 for total smoking habits and 2.17 for smoking at home), but no trend was apparent. Those who reported smoking for 30–39 years and 40 years or more had much lower OR that were not statistically significant.

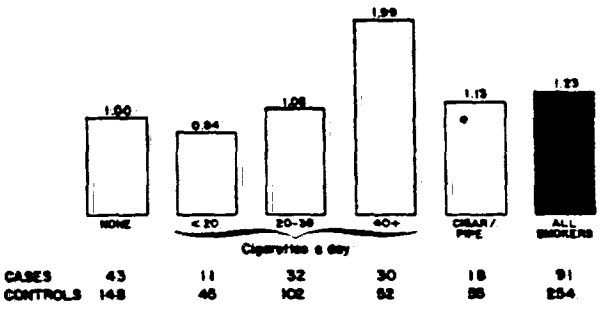
Table 6 shows OR for exposure categories by age group, histologic type of lung cancer, identity of the respondent who was interviewed, and socioeconomic status. Data are for average exposure for the last 5 years, for the last 25 years, by husband's total smoking habit, and by his smoking habits at home. OR generally were higher for those 70 years of age or over, for those with adenocarcinoma, when someone not in the immediate family was the respondent, and for those in the lower or lower middle class. There does not appear to be a pattern of high OR for any of these subgroups in all 4 exposure categories. Some of the OR are statistically significant, but they usually carry very wide CL with them.

Table 7 shows the OR for classification of exposure of women to smoke at home, at work, and in other areas, as compared with those women not exposed at all. OR for exposure at work during the last 5 years was 0.88; for the last 25 years, it was 0.93. The highest OR observed was 1.77 for exposure during the last 5 years in "other areas." None of the RR shown in this table are statistically significant.

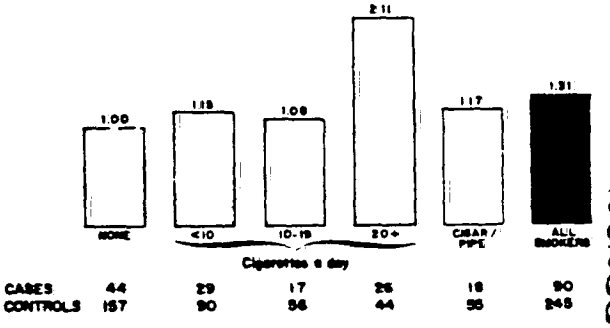
One of the questions in the interview was with regard to exposure to smoke in childhood. Those women who replied that they had been exposed in childhood had an RR of 0.91 (CL: 0.74, 1.12).

LOGISTIC REGRESSION ANALYSIS

An unconditional logistic regression model was used—which included terms for age, hospital, socioeconomic status, and year of diagnosis—to account for possible confounding factors. Testing was done on each of the four exposure variables, three of which were used in the Mantel-Haenszel analysis: 1) exposure during the last 5



TEXT-FIGURE 1.—OR for exposure to husband's total smoking habits.



TEXT-FIGURE 2.—OR for exposure to husband's smoking habits at home.

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TABLE 6.—*OR for smoke exposure categories, by age group, histologic type of lung cancer, identity of respondent, and socioeconomic status*

Specification	No. of cases	Smoke exposure							
		Last 5 yr		Last 25 yr		Husband's smoking habits			
						Total		At home	
		OR	95% CL	OR	95% CL	OR	95% CL	OR	95% CL
Age, yr									
<60	33	0.96	0.65–1.42	1.00	0.63–1.51	1.19	0.72–1.98	1.30	0.75–2.26
60–69	28	0.82	0.57–1.19	0.55	0.41–0.73	1.20	0.66–2.19	1.42	0.70–2.88
70–79	44	1.82	0.93–3.53	1.22	0.78–1.90	1.26	0.79–1.99	1.43	0.85–2.39
≥80	29	2.00	0.76–5.25	1.75	0.81–3.78	1.28	0.72–2.27	1.10	0.68–1.79
Histologic type									
Adenocarcinoma	87	1.43	0.99–2.06	1.15	0.85–1.56	1.33	0.94–1.87	1.48	1.01–2.17
Squamous cell carcinoma	11	1.28	0.52–3.19	0.85	0.43–1.69	5.00	1.28–19.33	5.00	1.43–20.18
Large cell carcinoma	21	0.55	0.41–0.74	0.67	0.47–0.94	0.76	0.51–1.13	0.62	0.45–0.86
Mixed and other	15	2.29	0.57–9.10	2.67	0.41–17.35	0.81	0.48–1.37	1.00	0.53–1.77
Respondent									
Self	16	1.96	0.62–6.17	0.91	0.51–1.60	0.83	0.50–1.38	1.00	0.55–1.74
Husband	34	1.00	0.67–1.52	0.46	0.38–0.55	0.77	0.56–1.06	0.92	0.63–1.34
Daughter or son	48	0.92	0.67–1.26	1.41	0.85–2.36	3.57	0.84–15.28	3.19	0.91–11.19
Other	36	2.23	0.90–5.54	2.23	0.83–5.96	1.58	1.11–2.67	0.77	0.57–1.03
Socioeconomic status									
Upper and upper middle class	6	1.60	0.31–8.19	1.50	0.34–6.59	1.23	0.36–4.18	1.50	0.34–6.59
Middle class	75	0.78	0.63–0.97	0.92	0.71–1.19	1.15	0.84–1.59	1.21	0.87–1.69
Lower and lower middle class	53	2.58	1.10–6.01	1.45	0.86–2.44	1.23	0.83–1.84	1.45	0.88–2.38

years, 2) exposure during the last 25 years, 3) husband's smoking at home, and 4) husband's smoking outside the home. The latter variable was used rather than the husband's total smoking as a check of the validity of exposure to husband's smoke and was derived by subtracting the number of cigarettes smoked at home from the total number of cigarettes the husband smoked per day. Each of these factors was tested as a continuous exposure variable—the most powerful technique for detecting any true underlying risk.

Table 8 shows the results of this analysis. Exposure for 5 years and 25 years had negative coefficients. The test for cigarettes smoked by husband at home showed a positive trend of increasing risk with increasing exposure and was statistically significant, with a *P*-value (one tailed) of .032. The test for cigarettes smoked outside the home was not statistically significant. The table also shows estimates of RR at the 10 hours per day exposure level and at 20 cigarettes per day smoked by the husband. The RR from exposure to 20 cigarettes/day smoked at home was 1.70; outside the home, it was 1.26. RR from exposure during the last 5 years and during the last 25 years were less than 1. A separate analysis that included respondent identity did not change the results materially.

TABLE 7.—*Number of cases and controls exposed to smoke of others at home, at work, and in other areas*

Variable	Smoke exposure			
	None	At home	At work	In other areas
Last 5 yr				
No. of cases	80	37	14	13
No. of controls	262	99	52	24
OR	1.00	1.22	0.88	1.77
95% CL		0.92–1.62	0.66–1.18	0.93–3.38
Last 25 yr				
No. of cases	42	73	34	19
No. of controls	135	204	118	43
OR	1.00	1.15	0.93	1.42
95% CL		0.89–1.49	0.73–1.18	0.89–2.26

TABLE 8.—*Logistic regression model[a] for involuntary smoke exposure variables, on continuous dose-response basis*

Variable	Coefficient (SE)	*P*-value[b]	Smoke exposure level	RR[c]
5-yr exposure to smoke	−0.0069 (0.0035)	0.422	10 hr	0.93
25-yr exposure to smoke	−0.016 (0.031)	0.303	10 hr	0.85
Cigarettes smoked at home	0.026 (0.014)	0.032	20 cigarettes	1.70
Cigarettes smoked outside home	0.012 (0.010)	0.127	20 cigarettes	1.26

[a] Model includes terms for age, hospital, socioeconomic status, and year of diagnosis.
[b] One tailed.
[c] Relative to the nonexposed woman.

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DISCUSSION

In a previous paper (*1*) the problem of classifying involuntary smoking on the basis of the husband's smoking habit was discussed. It was pointed out that questions directed at ascertaining a quantitative estimate of the number of hours a day that subjects were exposed might be a better measure than the total number of cigarettes that the husband smoked, inasmuch as not all of the husband's smoking was done at home. In the present study we classified the exposure both ways: by the number of hours per day the subjects were exposed to smoke of others and by the husband's smoking habits. We also recorded the respondent's estimate of how many cigarettes a day the husband smoked at home. In this group of women, husbands who smoked cigarettes smoked an average of 27 cigarettes a day, of which 11.5 cigarettes on average (43%) were smoked at home. Of course, all cigarettes smoked at home were not necessarily smoked in a room where the subject could have been exposed. In this study, the husband's smoking at home was related to the women's lung cancer, whereas number of hours of exposure a day to all sources of tobacco smoke was not related.

A potential source of error was the hospital's report of whether the subject smoked or not. In this study, 40% of the women with lung cancer, classified as nonsmokers (or smoking not stated) on the hospital record, were smokers at some time (table 1). Another 13% did not have primary lung cancer. It is apparent, therefore, that in any study of involuntary inhalation and lung cancer, the smoking histories of the subjects have to be confirmed as well as the extent of their involuntary exposures. Smoking histories of husbands were obtained for the 113 women who were smokers. The distribution by smoking habit is shown in table 9. As we might have expected, smokers are more likely to be married to smokers than are nonsmokers. The table shows that 43 of 134 women, or 32.1%, of the cases included as never smoked in this study had husbands who never smoked; but only 21 of 113, or 18.6%, of women who smoked and were mistakenly classified as nonsmokers in the hospital record had husbands who did not smoke. Among the controls only 8.5% of women who were called nonsmokers (or smoking was not stated) were smokers.

The table shows the effect on the OR, when one assumes that 8.5% of the additional controls needed for the 1:3 match had husbands with the same smoking distribution as the husbands of cases who were smokers, and that the balance had the same distribution as that of the 402 controls included in the study. The OR for the husband's smoking increase to 1.61 overall and are as high as 1.63 for the 20–39 cigarette a day smokers and 2.32 for the women whose husbands smoked 40 or more cigarettes a day. For exposure to the husband's smoke at home, the OR are 1.66 overall, 1.53 for women whose husbands smoke 10–19 cigarettes a day, and 2.85 for those whose husbands smoke 20 or more a day at home. Thus the inclusion of women whose smoking habits have not been reviewed greatly increases the OR.

TABLE 9.—*Hypothetical OR resulting from combining women in study with women originally classified as nonsmokers but who actually smoked*

Variable	Husband's total smoking habits						
	None	Cigarettes/day			Cigar and/or pipe	All types of smoking	Totals
		<20	20–39	≥40			
No. of cases							
Nonsmokers (in study)	43	11	32	30	18	91	134
Smokers (originally called nonsmokers)	21	9	43	24	16	92	113
Total (unscreened)	64	20	75	54	34	183	247
No. of controls							
Nonsmokers (in study)	148	45	102	52	55	254	402
Additional controls*	119	38	90	45	47	220	339
Total (unscreened)	267	83	192	97	102	474	741
OR	1.00	1.01	1.63	2.32	1.39	1.61	
	Husband's smoking habits at home						
	None	Cigarettes/day			Cigar and/or pipe	All types of smoking	Totals
		<10	10–19	≥20			
No. of cases							
Nonsmokers (in study)	44	29	17	26	18	90	134
Smokers (originally called nonsmokers)	23	22	22	30	16	90	113
Total (unscreened)	67	51	39	56	34	180	247
No. of controls							
Nonsmokers (in study)	157	90	56	44	55	245	402
Additional controls*	126	75	52	39	47	213	339
Total (unscreened)	283	165	108	83	102	458	741
OR	1.00	1.31	1.53	2.85	1.41	1.66	

* Upon reinterview, 8.5% of the controls were found to be smokers. They were distributed according to the smoking distribution of husbands of cases who were smokers. The balance were distributed according to the smoking habits of controls in the study.

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The classification used in this study might be criticized because some women married to ex-smokers could be counted in the same exposure category as a woman exposed to smoke up to the time of her final illness. However, all patients who have gone through diagnosis and treatment for lung cancer had some period of time when they were not exposed to others' smoke, either before or after treatment. We believe that the classification we used was indicative of the "usual amount of smoke to which the person was exposed." To determine the experience of a "pure" nonexposed group, 17 cases and 56 controls in this study were identified who were not exposed to the smoke of others during the last 5 years, during the last 25 years, whose husbands never smoked at home or elsewhere, and who never were exposed to smoke in their childhood. These cases and controls were compared with all other subjects. The OR was 1.14 (CL: 0.81, 1.59).

In conclusion, we found an elevated risk of lung cancer, ranging from 13 to 31%, in women exposed to the smoke of others, although the increase was not statistically significant. The women who were married to smokers of 40 or more cigarettes a day or who were exposed to the smoke of at least 20 cigarettes a day at home showed a risk twice as high as that of women not exposed at all. This result is consistent with the dose-response risk of exposure to the husband's smoke shown in some case-control studies (*2*, *3*). A dose-response relationship was confirmed in a logistic regression analysis. The lack of a relationship when exposure was classified by hours exposed to smoke of others may have occurred because this variable does not accurately measure intensity of exposure. There is no consistently higher risk for certain age groups or by histologic types, or by exposure at home or at work. Exposure in other areas carried a higher OR, but this finding is difficult to interpret.

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Lam, W.K., A Clinical and Epidemiological Study of Carcinoma of Lung in Hong Kong, M.D. thesis submitted to University of Hong Kong, 1985 (only some pages available).

In a case-control study of female adenocarcinoma in Hong Kong, 163 hospitalized cases and 185 hospitalized controls were interviewed. Exposures investigated included ETS, domestic cooking (including use of kerosene stoves), and home incense burning.

No RRs were presented; the author claims that no association was found for kerosene stove fumes and home incense burning and central or peripheral adenocarcinoma. "Passive smoking" was reportedly not associated with central adenocarcinoma, but was suggested to be associated with peripheral adenocarcinoma, particularly "passive smoking" due to smoking husbands.

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In Hong Kong, lung cancer is the commonest lethal malignant disease in both males and females. This thesis represented the first major clinical study of lung cancer (1979-1984) in the local Chinese population.

The patients were those admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, and all had histologically or cytologically proven lung cancer. Histological typing was based on the World Health Organization Classification (1981), with 4 major types of lung cancer, namely (1) squamous cell carcinoma (SQ), (2) small cell carcinoma (SM), (3) adenocarcinoma (AD), and (4) large cell carcinoma (LA).

A prerequisite for a clinical study of lung cancer is accurate cell typing. My phase-one study was to assess collaborately with the Department of Pathology the cell typing accuracy of cytodiagnosis (bronchoscopic and sputum) in our hospital. In a five-year study period (1979-1983) in 573 patients, for both bronchoscopic and sputum cytologic cell typing, accuracy was highest in SQ and SM (76-100%), followed by AD (80-88%). That of LA was much lower (< 67%), but the number of patients was small.

The next phase is collection of clinical data base by a clinical review of 493 patients admitted from 1976 to 1980. The male to female sex ratio was low (1.87:1), reflecting the

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high incidence of lung cancer in women in Hong Kong. In men, SQ was the predominant cell type (44%), followed by AD (23%), SM (13%) and LA (7%), but in women, the preponderance of AD (44%; SQ 31%; SM 10%; LA 2%) is noteworthy. Cigarette smoking was a major factor in SQ and SM. The relative risk of lung cancer in smokers was 6.4 to 10.7 for SQ and SM, but was not significant with AD or LA (< 1.8). SQ and SM, being smoking-related, showed features of a centrally located tumour. Our AD, contrary to classical teaching, also showed clinical, radiological and bronchoscopic features of a centrally situated tumour.

A three-part study was then carried out in parallel from 1981 to 1984 :

(1) Clinical data were collected from 503 patients upon diagnosis from January 1981 to April 1984. The findings of the review study were confirmed. The male to female ratio was low (1.96:1). A history of cigarette smoking was strongly associated with SQ and SM. The relative risk of lung cancer in smokers was 5.8 with SQ and 21 with SM in men, and 10.5 with SQ and 33.9 with SM in women, but not excessive with AD and LA (1 to 2.1). In women, AD was the predominant cell type (56%), and 46% of all cases and 63% of AD were life-long non-smokers. Again, AD showed features of a predominantly centrally situated tumour.

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(2) That our AD, usually in non-smoker females and centrally situated, was intriguing. A case-control study of 163 female patients and 185 female controls was carried out to compare their exposure to three common environmental, inhaled substances, namely passive smoking, kerosene stove fumes and home incense burning. Analysis for non-smokers showed that kerosene stove and incense burning were not contributory factors ($p > 0.05$). Passive smoking was also not shown to be associated with AD of the central type, but may contribute to AD of the peripheral type ($p < 0.05$).

(3) The median survival of our patients with untreated, inoperable disease was poor, being 1 month for small cell cancer and 3.5 months for non-small cell cancers. We studied the effect of three combination chemotherapy schemes on survival of these patients. In 43 patients of small cell carcinoma, MACC (methotrexate, adriamycin, cyclophosphamide and CCNU) chemotherapy was effective (21% complete and 53% partial response), and significantly improved overall patients survival (median survival 50 weeks). In non-small cell cancers, however, MACC chemotherapy (in 42 patients) and FuAM/FiAM schemes (Futraful/5-Fluorouracil, adriamycin, mitomycin-C, in 44 patients of adenocarcinoma), were ineffective. Although partial response occurred in 5-27% of patients, there was no overall survival benefit.

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With a more solid data base, collaborative studies are now being initiated, including city-wide epidemiological studies, clinico-pathologic studies, and studies of host determinants.

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families, and should therefore be re-examined.

C. Incense Burning at Home - Burning of Chinese incense at temples in worship of idols or gods, a common scene in tourists books, is part of the traditional Chinese customs still practised in Hong Kong. Burning of incense at home, either for ancestor worship (traditional Chinese filial piety) or deity worship, is also common among the large non-Christian local population. Chinese incense smoke has been shown to contain carcinogens, (Schoental & Gibbard, 1967) but to-date, no studies have been undertaken to examine its relation to lung cancer. Given that (1) in Hong Kong, home incense burning is common, (2) that many adult women in Hong Kong are housewives who spend most of their time at home, inhaling incense smoke which contains carcinogens, & (3) that Hong Kong is overcrowded with many families living in houses/flats of area 400 to 800 square feet only, which would increase the inhaled dose of any potential "inhaled carcinogen" present in a small home area, it is conceivable that incense smoke might well be important in the genesis of lung cancer in our women who do not smoke.

A study was therefore carried out to examine whether passive smoking, kerosene stove cooking and incense burning at home are likely causative factors in lung cancer in non-smoking Chinese women. This forms Part C of the 1981-1984 lung cancer

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study, (see Chapter 5, pp 69).

7.2 Patients & Methods

This is a case-control study. The cases were all of the Chinese female patients who were admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984, with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types (Types 1-4, W.H.O. Classification, 1981). Great care was taken to exclude secondary carcinoma of the lung (see pp 18-19) but otherwise all Chinese female patients were included with no other selection criteria. Comparison patients (controls) were Chinese female patients admitted to the Orthopaedic wards in Queen Mary Hospital during the period 1982-1984, comparable to lung cancer patients in age and social class - both cases and controls were patients of the third class general wards and were mostly from the lower income group. Patients with pathological fractures due to smoking-related malignancies, and peripheral vascular disease-related orthopaedic conditions were excluded. It is considered that our orthopaedic controls should not be biased towards smoking-associated diseases.

All cases were interviewed by myself, and the controls by myself or Miss Cindy Ling, our technician and research assistant, who was trained for this investigation and thoroughly

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familiar with local culture. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking including kerosene stove, and home incense burning, in form of a standardized questionnaire (Fig. 7.1). For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, arrangement would then be made for their next-of-kin to be interviewed with the patients as interpreter.

Attempts at quantitation of passive smoking has been recognised as difficult (Royal College of Physicians, 1983; Weiss et al, 1983). Sidestream smoke, to which the passive smoker is exposed, is diluted by room air to a variable extent. The room air itself also contains smoke which has been inhaled and then exhaled into the air. Amount and duration of smoke exposure, the smokers' smoking habit, size and ventilation of rooms etc. are all important variables, and the amount of the various components of tobacco smoke breathed by the non-smoker from a smoky atmosphere are therefore extremely variable and unpredictable, and there are no agreed standards for expressing the extent of pollution of indoor atmospheres by tobacco smoke. The same problem applies to quantitation of exposure to kerosene stove cooking fumes and burning of incense at home. I had the opportunity of discussing this with Sir Richard Doll during his visit to the University Department of Medicine, Hong Kong, in

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FIG. 7.1. LUNG CANCER QUESTIONNAIRE

Name: _____ Sex/Age: _____ Date _____

Address (District): _____ How Long? _____ Dx: _____

Born in ☐ Hong Kong ☐ China In Hong Kong for ____yrs. Dialect Gp. _____

Occupation: _____ for _____ yrs. Schooling ☐ ≤ 6 yr. ☐ > 6 yr.

Marital Status: ☐ Single ☐ Married ☐ Widowed _____ yrs.

Husband: occupation _____

SMOKING: ☐ non-smoker ☐ ex-smoker _____ yrs. ☐ smoker

☐ cigarettes ☐ hand-rolled ☐ water-pipe ____/day x ____ yrs.

PASSIVE SMOKING:

Home: Size of home: _____ No. family members: _____

	Husband	Others		Father	Mother
Non-smoker	☐	☐	☐	☐	☐
Smoker: Amount	_____/day	_____/day	____/day	_____/day	___/day
Exposure/d	_____ hr.	_____/hr.	____/hr.	_____/hr.	___/hr.
Duration	_____ yr.	_____/yr.	_____/yr.	_____/yr.	___/yr.

AT WORK: Size of working place _____ No. of smoker workmates _____

Exposure time/day _____ hr. for _____ yrs.

DOMESTIC COOKING: ☐ Never/seldom cooks

☐ Cooks regularly

☐ Kerosene _____ yrs. ☐ Electricity _____ yrs.

☐ Coal gas _____ yrs. ☐ Gas _____ yrs. ☐ wood ____ yrs.

Chinese pan cooking ☐ yes ☐ no ____ times/wk for ____ yrs.

HOME INCENSE BURNING: ☐ Yes ☐ No for _____ yrs.

☐ Daily ☐ Festivals only

☐ Inside house ☐ Outside house

HISTORY OF PULMONARY TB: ☐ Yes ☐ No

Chest x-ray: (No.)

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November 1983, and he advised that it would be best to categorize exposure as positive and negative only with no further attempts at quantitation.

The significance level for the risk ratios are calculated for 2 tests, Test A and Test B. Test A is whether the risk-ratio is really greater than one, using the Bayesian risk ratio analysis method by Altchison and Bacon-Shone (1981). Test B uses a logistic regression model (Breslow & Day, 1980):

$$\log \frac{P\ (\text{cancer/risk})}{P\ (\text{no cancer/risk})} = \alpha + \beta \times \text{exposure}$$ (P : Probability)

The test is of whether $\beta > 0$, i.e. that the chance of cancer increases with exposure.

7.3 Results

A total of 163 cases and 185 controls were interviewed. Two cases (both were chronic smokers with small cell carcinoma) were too ill to be interviewed, and we failed to arrange meeting their relatives, and they were excluded from the study. Of the 185 controls, 80 were treated for fractures, 17 for infective bone and joint diseases (including tuberculosis), 15 for osteoarthrosis, 8 for rheumatoid arthritis, and 65 for other orthopaedic conditions.

Demographic characteristics of the cases and controls are compared in Table 7.1. The groups are similar in age, as

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indicated by the distribution in Table 7.1, and medians of 67.5 years for cases and 66 years for controls. Socioeconomic status (as measured by occupation, years of schooling) and recent residence are also similar in both groups. It is therefore considered not necessary to stratify these variables in the analysis.

The cases and controls' smoking habit was obtained in detail as described on pp 86-87, Chapter 5, and the results were presented in Table 5.8, pp 89, which is reproduced here as Table 7.2 for easy reference. The results were discussed in Chapter 5.

There were a total of 75 non-smokers in the cases and 144 non-smokers in the controls, and they form the study population for the present analysis.

No attempts at quantitation (except for Test B) was made as described above in Methods. When passive smoking (P), kerosene (K) and incense (I) were considered together, three intersecting circles can be drawn showing seven possible combinations of exposure, and one isolated circle (N) indicating those who had never been exposed to any of these sources (Fig. 7.2). Passive smoking includes exposure to smoking husbands, cohabiting relatives, or workmates.

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TABLE 7.1.

DEMOGRAPHIC CHARACTERISTICS OF THE CASES & CONTROLS

	Cases		Controls	
	No.	(%)	No.	(%)
Number	161		185	
Age (median, years)	(67.5)		(66)	
≤ 49 years	18	(11)	19	(10)
50-69 years	74	(46)	98	(53)
≥ 70 years	69	(43)	68	(37)
Places of origin from the southern province of Guangdong *	147	(91)	155	(84)
Never married	16	(10)	14	(8)
Occupation				
Housewife	95	(59)	134	(72)
Domestic servant	32	(20)	22	(12)
Labour/factory/hawker	31	(19)	25	(14)
Office/nurse/teacher	3	(2)	4	(2)
Schooling of ≥ 6 years	26	(16)	20	(11)
Recent residence				
Urban	150	(93)	177	(96)
Semi-urban/rural **	7	(4)	5	(3)
Boat (Fisherman)	4	(2)	3	(2)

* please see Fig 2.1, pp

** the New Territories (excluding the new satellite towns), and outlying islands.

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TABLE 7.2. CELL TYPE OF LUNG CANCER AND SMOKING HABIT IN 163 FEMALE PATIENTS WITH TYPES I-IV LUNG CANCER, 1981-1984

Type	I		II		III		IV		Controls
	No. (%)	RR	No. (%)	RR	No. (%)	RR	No. (%)	RR	No. (%)
Non-smoker	7 (25)	1	3 (9)	1	60 (62)	1	5 (71)	1	144 (78)
< 19 pack-yr	5 (18)		3 (9)		9 (9)		0 (-)		19 (10)
20-39 pack-yr	8 (29)		15 (47)		19 (20)		1 (14)		14 (8)
> 40 pack-yr	8 (29)		11 (34)		8 (8)		1 (14)		8 (4)
All smoker	21 (75)	10.5	29 (91)	33.9	136 (38)	2.1	2 (29)	1.4	41 (22)
TOTAL	28		32		96		7		185

I : Squamous cell; II : Small cell; II : Adenocarcinoma; IV : Large cell

RR : Relative risk, calculated as $\frac{\text{No. of smokers in cancer group}}{\text{No. of non-smokers in cancer group}} \times \frac{\text{No. of non-smokers in controls}}{\text{No. of smokers in controls}}$

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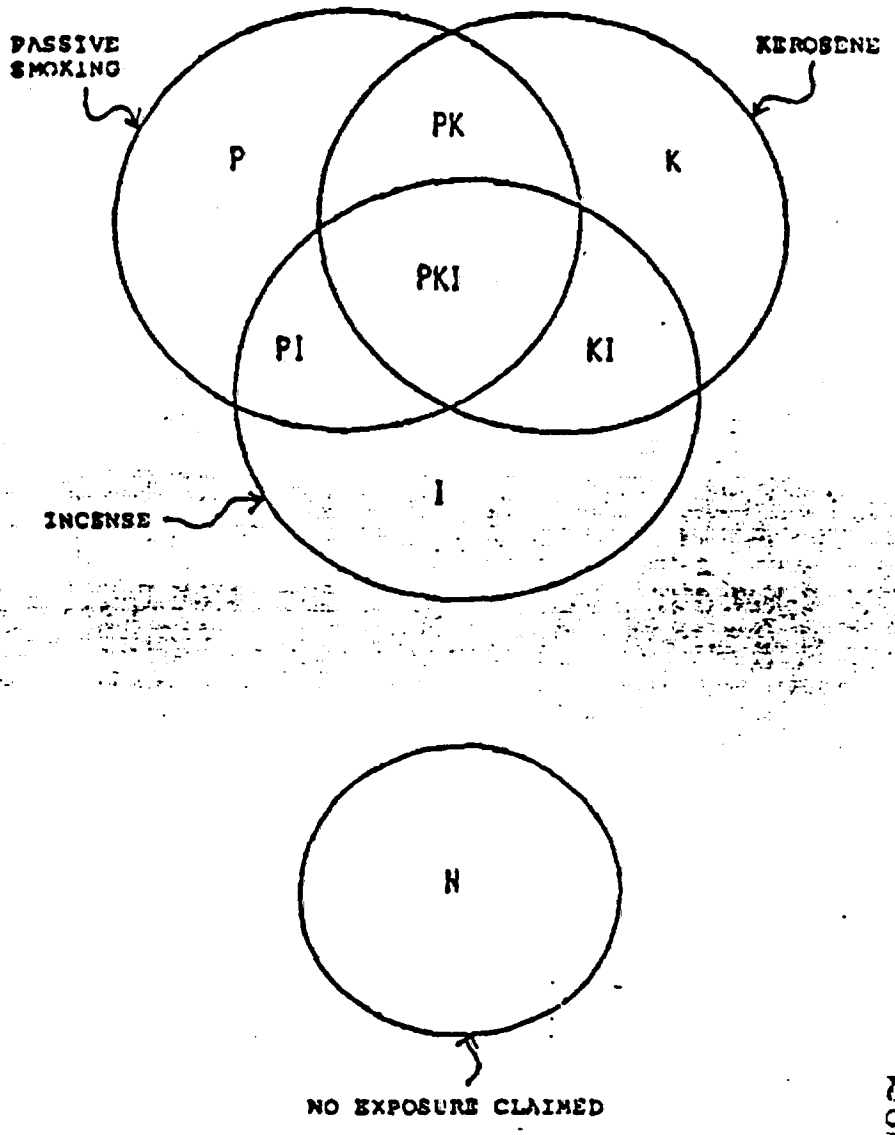
FIG. 7.2.

EXPOSURE CATEGORIES TO PASSIVE SMOKING, KEROSENE AND INCENSE



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The number of non-smoking cases with types 1 (squamous cell), 2 (small cell) and 4 (large cell) lung cancer are small -- being seven, three and five respectively (Table 7.3), and did not therefore afford meaningful statistical analysis. For type 3 adenocarcinoma, the pathogenesis of which we are most interested in, there were 60 non-smokers, and the proportions of different exposure categories are tabulated in Table 7.4. The cases are stratified into central and peripheral tumours to examine the contention that our preponderance of central adenocarcinoma might be related to inhaled carcinogens. The risk ratios (and their significance level) for exposure to passive smoking, kerosene and incense in our non-smoker adenocarcinoma female patients are shown in Table 7.5. Total passive smoking and passive smoking due to smoking husband alone are examined separately.

7.4. Discussion

The problem posed before us is the preponderance of adenocarcinoma of lung, usually in non-smokers, predominantly centrally situated, in our female population. This case-control study was carried out to compared exposure of cases and controls to three environmental, inhaled substances, namely passive smoking, kerosene stove cooking fumes and home incense burning fumes. The results showed that (Table 7.5) kerosene and incense

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TABLE 7.3.

DIFFERENT EXPOSURE CATEGORIES FOR TYPES 1, 2 & 4 LUNG CANCER IN NON-SMOKING WOMEN

Exposure* Category	No. of cases			No. of controls
	squamous cell (1)	small cell (2)	large cell (4)	
P	-	-	1	3
K	-	-	-	6
I	-	-	-	13
PK	3	1	-	21
PI	-	-	1	17
KI	-	-	-	35
PKI	4	2	3	40
N	-	-	-	9
Total	7	3	5	144

* please refer to Fig.7.2.

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TABLE 7.4.

DIFFERENT EXPOSURE CATEGORIES FOR ADENOCARCINOMA OF LUNG IN NON-SMOKING WOMEN

Exposure * Category	No. of cases		No. of controls
	Central	Periphoral	
P	1	-	3
K	3	1	6
I	-	1	13
PK	7	7	21
PI	5	6	17
KI	6	5	35
PKI	9	8	40
N	1	-	9
Total	32	28	144

* please refer to Fig.7.2.

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are not contributory factors for adenocarcinoma, central or peripheral. Although the risk ratio of passive smoking is greater than one for central adenocarcinoma, the level of significance is only about 10 per cent by Test A. There is however suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking due to smoking husbands. The differences between Tests A and B in Table 7.5 could be due to a non-linear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information.

There has been only one published report of passive smoking in female lung cancer patients in Hong Kong (Koo et al, 1983). Koo found that passive smokers as a group had a relative risk of less than one. 40 of the 56 non-smoker patients (71.4%) and 83 of the 85 non-smoker controls (74.1%) have been exposed to passive smoking, which is not statistically different. The patients however included all cell types and were heterogeneous in this sense. In addition, the author did not distinguish central and peripheral tumours.

The association of passive smoking and lung cancer should be further pursued. There is good theoretical support for the association. Recently, it was reported that, like active smokers, the passive smoker is exposed to the same

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radioclements in the tobacco, as 50 to 70 per cent of the ^{210}Po appears in sidestream smoke (Winters & DiFrenza, 1983). In addition, the exposure of the passive smoker to naturally occurring radon daughters is increased in a smoky environment. It was estimated that radon daughter exposure could account for 20 to 100 per cent of lung cancers seen in non-smokers (Harley & Pasternack, 1981; Winters & DiFrenza, 1983). The conflicting findings of the Japanese (Hirayama, 1981) and American (Garfinkle, 1981) studies might be due to differences in methodology (Weizz et al, 1983). A potentially important factor is that the American study lacked smoking data on 73% of the husbands of nonsmoking women in comparison to only 28% in the Japanese study, which may have created biases in the data. A greater number of working women, larger homes and a higher divorce rate in the United States are other factors that could serve to account for the differences in results between these studies. In Hong Kong, the problem of overcrowding is notorious, with many families living in houses/flats of area 400 to 800 square feet only, and this would increase the inhaled dose of any potential inhaled carcinogen present in home environment. Previous estimates would have estimated the attributable risk of lung cancer due to passive smoking to be 30% greater in non-smokers exposed regularly to passive smoke

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compared to nonsmokers not exposed (Leeds, 1978). It has been found that both the Japanese and the American studies were in fact consistent with such an effect (Weiss, 1983).

The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumours) in our patients is unexpected, and the reason unclear. It is known however that there is a difference in chemical composition of mainstream and sidestream smoke (Stock, 1980; Correa et al, 1983; Weiss et al 1983). Mainstream smoke emerges into the environment after having been drawn through the cigarette, filtered by the smoker's own lungs, and then exhaled. Sidestream smoke arises from the burning end of the cigarette and enters directly into the environment. All these lead to marked differences in the concentration of the constituents of mainstream and sidestream smoke, and many potentially toxic gas phase constituents, including nitrosamine, are in higher concentration in sidestream smoke than in mainstream smoke, and nearly 85% of smoke in room results from sidestream smoke (Weiss et al, 1983). It is true, of course, that sidestream smoke is generally diluted in a considerably larger volume. Thus, passive smokers are exposed to a quantitatively smaller and qualitatively different smoke exposure than active smokers. Whether this might produce different proportion of histological

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types of tumour (preponderance of adenocarcinoma), with peripheral location remains, at present, conjectural.

Two of the limitations of the present study are the relatively small number of subjects studied, and the inclusion of only one hospital, albeit a large, regional general hospital. Large, city-wide multi-hospital studies are warranted, and we are currently overcoming the immense logistic problems and pursuing further collaborative studies in this area (vide infra).

7.5. Conclusion

1. Our results showed that kerosene stove fumes and home incense burning are not contributory factors for adenocarcinoma of lung, whether central or peripheral. Passive smoking is also not shown to be associated with adenocarcinoma of the central type. The reason for the preponderance of central adenocarcinoma in our non-smoker female patient population has therefore remained unanswered.

2. There is however suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking due to smoking husbands. The reason for the peripheral location of the associated tumour is

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not clear, although it is known that passive smokers are exposed to a qualitatively different smoke as compared to active smokers.

3. These findings need to be confirmed by large, city-wide, multi-institutional studies.

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Wu, A.H., Henderson, B.E., Pike, M.C. and Yu, M.C., "Smoking and Other Risk Factors for Lung Cancer in Women," Journal of the National Cancer Institute 74(4): 747-751, 1985.

A total of 149 white women diagnosed with adenocarcinoma (ADC) and 71 with squamous cell carcinoma (SCC) were included in this case-control study carried out in Los Angeles county, California. The purpose of the study was to investigate the roles of several potential etiological factors in female lung cancer. One individually matched neighborhood control was selected for each interviewed case. The questionnaire employed included personal smoking habits, exposure to "passive tobacco smoke," lung diseases, dietary intake of vitamin A, types of heating and cooking fuels used, reproductive history and employment history. Regarding ETS, questions were asked about smoking in the household during childhood, spousal smoking and smoking by other household members during adulthood, and average number of hours/day of exposure at the workplace.

Of the total, only 29 ADC and 2 SCC cases were nonsmokers. RRs were presented for the ADC cases: smoking by parents, RR = 0.6 (95% CI 0.2-1.7), spousal smoking, RR = 1.2, (95% CI 0.5-3.3) and workplace exposure, RR = 1.3 (95% CI 0.5-3.3).

Regarding confounders, history of lung disease before age 16 was reportedly statistically significantly associated with ADC (RR = 2.7, 95% CI 1.1-6.7). Elevated RRs were also reported for exposure to burning coal used for heating or cooking during childhood and teenage years. A significantly increased ADC risk was reported for the lowest level of beta-carotene consumption; however, no associations were reported for an index of total preformed vitamin A or for total vitamin A intake.

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Smoking and Other Risk Factors for Lung Cancer in Women [1,2]

Anna H. Wu, *Ph.D.*,[3] Brian E. Henderson, *M.D.*,[3] Malcolm C. Pike, *Ph.D.*,[3,4] *and* Mimi C. Yu, *Ph.D.*[3,5]

ABSTRACT—A case-control study among white women in Los Angeles County was conducted to investigate the role of smoking and other factors in the etiology of lung cancer in women. A total of 149 patients with adenocarcinoma (ADC) and 71 patients with squamous cell carcinoma (SCC) of the lung and their age- and sex-matched controls were interviewed. Personal cigarette smoking accounted for almost all of SCC and about half of ADC in this study population. Among nonsmokers, slightly elevated relative risk(s) (RR) for ADC were observed for passive smoke exposure from spouse(s) [RR=1.2; 95% confidence interval (CI)=0.5, 3.3] and at work (RR=1.3; 95% CI=0.5, 3.3). Childhood pneumonia (RR=2.7; 95% CI=1.1, 6.7) and childhood exposure to coal burning (RR=2.3; 95% CI=1.0, 5.5) were additional risk factors for ADC. For both ADC and SCC, increased risks were associated with decreased intake of β-carotene foods but not for total preformed vitamin A foods and vitamin supplements.—JNCI 1985; 74:747-751.

Lung cancer is now the fourth most common cancer in women (*1*) and has been projected to be the leading cause of cancer mortality among women by the mid-1980's (*2*). Causes of lung cancer, other than cigarette smoking (*3*), have not been clearly identified, but associations with exposure to passive smoking (*4–6*), exposure to combustion products of heating and cooking fuels (*7*), and occupational exposures (*8–10*) have been suggested. In addition, lung "scarring" (*11*) and a low dietary intake of β-carotene (*12–14*) and preformed vitamin A (*15–17*) may increase the risk of lung cancer.

This paper reports a case-control study of ADC and SCC of the lung in white females in Los Angeles County. Each of the above-mentioned factors was investigated.

METHODS

Female patients diagnosed with primary ADC or SCC of the lung were prospectively identified by the CSP, the population-based tumor registry for Los Angeles County (*18*), between April 1, 1981, and August 31, 1982. On the basis of information collected routinely by the CSP, we limited eligibility to white Los Angeles County residents, with no history of cancer (other than non-melanoma skin cancer) and under age 76 at diagnosis; we verified these variables at interview. We also excluded cases if they were born outside the United States, Canada, or Europe; were not English-speaking; or were not residents of Los Angeles County at the date of diagnosis.

A total of 490 eligible cases were identified. Of these patients, 190 had died or were too ill to participate by the time we contacted their attending physician. Permission was granted to contact 272 of the remaining 300 patients. Eight patients were not located, and 44 refused to be interviewed so that we obtained completed questionnaires on 220. On the basis of information on the CSP abstract, no significant differences were noted between those interviewed and those not interviewed in terms of age, marital status, religion, and smoking status recorded on medical records. However, those who were not interviewed were more likely to have distant metastases at the time of diagnosis (58%) compared to those who were interviewed (11%). Comparable percentages of eligible SCC (43%) and ADC (46%) patients were interviewed.

We selected one individually matched neighborhood control for each interviewed case. The control had to fulfill all the criteria given above for cases (with reference date taken to be the same as that of the matching case) and, in addition, was matched with the case on date of birth (±5 yr of birth date). Our control selection algorithm defined a specified sequence of houses to be visited in the neighborhood where the case lived at date of diagnosis. Our goal was to interview the first eligible resident in this sequence. If no one was home at the time of the visit, we left an explanatory letter and made a follow-up visit after several days. For any patient, 80 housing units were visited and 5 return visits were made before failure to secure a matched control was conceded. In 150 instances the first eligible person agreed to participate, in 55 instances the second eligible control in the sequence was interviewed, and in 15 instances the third eligible control was interviewed.

Cases and controls were interviewed on the telephone with the use of a structured questionnaire designed to elicit information on personal smoking habits, exposure to passive tobacco smoke, lung diseases, dietary intake of vitamin A, types of heating and cooking fuels ever used, and reproductive history. We also obtained a lifetime history of all jobs (job title, activities, and exposure) of at least 6 months' duration.

For childhood passive smoking exposure, we asked about the smoking habits (i.e., amount and years of smoking) of father, mother, or other household members

Abbreviations used: ADC=adenocarcinoma; CI=confidence interval; CSP=University of Southern California/Los Angeles County Cancer Surveillance Program; RR=relative risk(s); SCC=squamous cell carcinoma.

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[2] Supported by grant S163 from the American Cancer Society.

[3] Department of Family and Preventive Medicine, University of Southern California School of Medicine, Parkview Medical Building B, 2025 Zonal Ave., Los Angeles, CA 90033.

[4] *Present address:* Imperial Cancer Research Fund's Cancer Epidemiology Unit, Radcliffe Infirmary, Oxford University, Oxford OX2 6HE, England.

[5] We thank the word-processing pool for preparation of the manuscript.

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when they lived with the respondent during her childhood and teenage years. For passive smoke exposure during adult life, we asked about the smoking habits of spouse(s) and other household members when they lived with the respondent. Passive smoke exposure at work was assessed only in terms of the average number of hours per day to which the respondent believed she was exposed at each job.

The questions on vitamin A intake specifically asked about average frequencies of consumption of 21 vegetables and fruits that are high in β-carotene and 7 foods that contained preformed vitamin A during the calendar year 3 years before diagnosis of the case (*19*). Pattern of use of vitamin supplements was also assessed for the same period. On the basis of U.S. Department of Agriculture tables of food values for standard portion size (common household measure) of each item (*20*), we estimated average daily intake of β-carotene (or vitamin A) by summing the product of the β-carotene (or vitamin A) content of each food item and its reported frequency of consumption. Quartiles of consumption were constructed on the basis of the intake pattern of the 220 controls.

All cases were diagnosed microscopically. Their routine pathology reports were reviewed for mention of lung scarring.

Statistical analysis was conducted with the use of multivariate logistic regression methods for individually matched case-control studies (*21*). RR were estimated by odds ratios. A case-control pair was excluded from any given analysis if the information for either the case or the control was not known for the relevant variable(s). Since personal smoking will often, if not always, confound other associations, RR for other factors were always given after adjustment was made for personal smoking.

For ADC, RR for certain factors were given separately for nonsmokers, ex-smokers, and current smokers; this was not done for SCC because the numbers of nonsmokers and ex-smokers were too few.

RESULTS

We interviewed 149 ADC and 71 SCC cases and their matched controls. The mean age at diagnosis was 59.7 years for ADC cases and 61.4 years for SCC cases. The mean ages (at date of diagnosis of the index case) for the respective control groups were 59.5 and 61.1 years.

Personal cigarette smoking.—For both ADC and SCC, there was a significant trend in risk associated with increasing number of cigarettes smoked per day and with decreasing age at which smoking began (table 1). Both aspects of smoking remained significant after adjustment was made for the other.

Passive smoking.—Families tended to share similar smoking behavior. Controls whose father, mother, or spouse(s) smoked were more likely to smoke, to be heavy smokers, and to start at a younger age than controls whose family members did not smoke. For ADC and SCC, after adjustment was made for personal smoking habits, there were no significantly increased risks for having a mother, a father, or spouse(s) who smoked or for being exposed at work (table 2).

For nonsmoking ADC cases, we did not observe any elevated risk associated with passive smoke exposure from either parents (RR=0.6; 95% CI=0.2, 1.7), from spouse(s) (RR=1.2; 95% CI=0.5, 3.3), or at work (RR=1.3; 95% CI=0.5, 3.3). Increasing RR (RR=1.0, 1.2, 2.0) were found with increasing years (0, 1–30, ≥31) of passive smoke exposure during adult life from spouse(s) and at work, but the results were not statistically significant. Since the exposures may have occurred concurrently, the years of exposure represent units rather than chronologic time of exposure.

Childhood exposures.—For both ADC and SCC, no significant association was found with history of lung diseases (specifically, asthma, bronchitis, pneumonia, tuberculosis, fungal diseases, emphysema, and lung abscess) diagnosed by a physician at least 5 years before diagnosis of the case. When the analysis was restricted to lung diseases that occurred before age 16 (childhood), a significantly elevated RR for pneumonia was observed for ADC after adjustment was made for personal smoking habits (RR=2.7; 95% CI=1.1, 6.7), and the RR for SCC (RR=2.9; 95% CI=0.5, 17.4) was in the same direction. Parental smoking did not explain this effect. Table 3 shows that for ADC, the effect of childhood pneumonia was most apparent among nonsmokers: Of the 25

TABLE 1.—*Personal smoking habits of cases and controls*

Smoking status	ADC			SCC		
	RR	95% CI	Case/control	RR	95% CI	Case/control
Nonsmoker	1.0		29/62	1.0		2/30
Ex-smoker*	1.2	0.6, 2.3	21/37	7.7	0.8, 70.3	8/18
Current smoker	4.1†	2.3, 7.5	99/50	35.3†	4.7, 267.3	61/23
Current smoker: No. cigarettes/day						
1–20	2.7	1.4, 5.4	38/28	17.7	2.3, 138.2	19/14
≥21	6.5†	3.1, 13.9	61/22	94.4†	9.9, 904.6	42/9
Current smoker: age started to smoke, yr						
≥25	1.1	0.4, 3.2	8/14	7.8	0.8, 73.7	6/5
19–24	2.5	1.0, 5.8	22/15	47.1	4.4, 498.5	18/7
≤18	8.0†	3.6, 17.9	69/21	115.7†	9.8, 1371.2	37/11

* Had stopped smoking at least 3 yr before diagnosis year of case.
† *P* (linear trend) <.001.

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TABLE 2.—*Exposure to passive smoking in cases and controls*

Smoking status	ADC		SCC	
	Adjusted RR[a]	95% CI	Adjusted RR[a]	95% CI
Mother smoked	1.7	0.8, 3.5	0.2	0.0, 1.5
Father smoked	1.3	0.7, 2.3	0.9	0.3, 2.9
Spouse(s) smoked[b]	1.2	0.6, 2.5	1.0	0.1, 7.6
Exposure at the workplace	1.2	0.8, 2.2	2.3	0.7, 7.9

[a] Adjusted for number of cigarettes smoked per day and age at starting to smoke.
[b] We eliminated from the analysis 15 pairs of ADC and 4 pairs of SCC in which either the case or the control was never married.

nonsmoking ADC cases, 8 (28%) gave a history of childhood pneumonia.

Elevated RR, adjusted for personal smoking habits, were observed for exposure to burning coal used for heating or cooking in a stove or fireplace during the majority of childhood and teenage years (ADC: RR=2.3; 95% CI=1.0, 5.5. SCC: RR=1.9; 95% CI=0.5, 6.5). For ADC, elevated RR were observed in each personal smoking habit category (table 3).

TABLE 3.—*RR and 95% confidence intervals of ADC of the lung according to childhood pneumonia and coal burning by personal smoking habits*

Exposure	RR (95% CI) among:		
	Nonsmoker	Ex-smoker	Current smoker
Childhood pneumonia[a]			
No	1.0	1.4 (0.6, 2.4)	5.1 (2.5, 10.3)
Yes	3.1 (1.0, 9.9)	1.5 (0.2, 10.8)	10.9 (2.1, 57.9)
Childhood coal burning[b]			
No	1.0	1.5 (0.6, 3.5)	6.3 (3.0, 13.3)
Yes	3.2 (0.9, 11.8)	4.3 (1.0, 17.8)	9.5 (2.1, 41.9)

[a] Before age 16. The analysis was based on 149 case–control pairs of ADC.
[b] Includes heating or cooking with coal burned in a stove or fireplace during childhood and teenage years. The analysis was based on 143 case–control pairs of ADC.

Dietary vitamin A.—Table 4 presents RR for ADC, adjusted for personal smoking habits, by quartiles of indices of vitamin A consumption. Because of the smaller sample size of SCC cases, the indices were dichotomized. For ADC, a significantly increased risk was observed only for those in the lowest quartile of β-carotene consumption (<2,000 IU/day) compared to those in the highest quartile (>4,000 IU/day), but no appreciably increased risks were observed for those in the intermediate groups. For SCC, an elevated, but not statistically significant, RR was observed for women with β-carotene intake below the median: When those in the lowest quartile of β-carotene consumption, i.e., less than 2,000 IU/day, were compared to those consuming more than 2,000 IU/day, the unadjusted RR was increased to 1.7 (from 1.3), but after adjustment the RR was not greater than comparisons above and below the median (both RR=1.5).

There was no association with an index of total preformed vitamin A (i.e., dairy products, eggs, liver, and vitamin supplements) for either cell type. However, for ADC and SCC, an association was observed for dairy products and eggs (table 4).

Other factors.—We could find no association between any occupation or occupational category and risk of ADC or SCC, but there was an excess number of cooks (4 cases and 2 controls) and beauticians (8 cases and 5 controls) among cases; both occupations have been suggested in previous studies. Elevated RR adjusted for personal

TABLE 4.—*Dietary intake of β-carotene, total preformed vitamin A, and dairy products and eggs among cases and controls*

Quartile	β-Carotene[a]		Total preformed vitamin A[b,c]		Dairy products and eggs[c]	
	Adjusted RR[d]	95% CI	Adjusted RR[d]	95% CI	Adjusted RR[d]	95% CI
ADC						
1 (high)	1.0		1.0		1.0	
2	0.8	0.3, 2.0	0.6	0.3, 1.4	1.7	0.8, 3.9
3	1.3	0.6, 2.7	1.1	0.5, 2.5	2.2	1.0, 4.8
4	2.5	1.1, 5.7	1.2	0.5, 2.8	2.7	1.2, 5.8
SCC						
1 and 2	1.0		1.0		1.0	
3 and 4	1.5	0.6, 3.8	1.0	0.4, 2.4	1.6	0.7, 3.9

[a] Includes 21 vegetables and fruits: leafy lettuce, other leafy green, broccoli, carrots, tomatoes, green peas, green beans, lima beans, asparagus, summer squash, winter squash, sweet potatoes and/or yams, green pepper, red pepper, hot red chili pepper, cantaloupe, watermelon, peaches, apricots, nectarines, and tomato and/or V8 juice. Analysis was based on 147 pairs of ADC and 69 pairs of SCC.
[b] Includes eggs, cheese, butter and/or margarine, cream, milk, beef and/or calf liver, chicken and/or turkey liver, and vitamin supplements.
[c] Analysis was based on 147 pairs of ADC and 71 pairs of SCC.
[d] Adjusted for number of cigarettes smoked per day.

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smoking habits were observed for a history of hysterectomy (RR=1.7; 95% CI=0.9, 3.2) and nulliparity (RR=1.7; 95% CI=0.8, 3.7) among ADC cases and a history of miscarriage (RR=1.5; 95% CI=0.5, 4.9) among SCC cases.

Multiple logistic regression analysis was conducted to assess the possible confounding effects of personal smoking habits, childhood pneumonia, childhood coal burning, and β-carotene intake. The results were similar to those when each factor was adjusted for personal smoking habits alone.

DISCUSSION

This case-control study examined risk factors for the two main cell types of lung cancer in women—ADC and SCC. Although histologic typing was done by the individual pathologist at each participating hospital, studies comparing interobserver and intraobserver variability in classification of lung cell types reported a high concordance rate for cell types other than large cell carcinoma, which was excluded in this study (*22, 23*).

In this study population, about half of ADC and almost all of SCC can be attributed to personal smoking habits; the amount smoked and the age at which smoking began were strong determinants of risk of disease. However, there are marked differences in the strength of association between smoking and cell type of lung cancer, as has been noted previously (*24, 25*).

The role of passive smoking in the etiology of ADC among nonsmokers is not clear. Our data are not consistent with the findings with regard to nonsmokers obtained by Hirayama (*4*) and Trichopoulos et al. (*5*) who reported a twofold to threefold increased risk due to passive smoking. However, the histology of the cases in these studies is not clear, and their data suggest that any effect of passive smoking is larger for SCC cases (*5, 6*). Of our 29 nonsmoking ADC cases, 12 were bronchoalveolar cell carcinomas, and this cell type is specifically mentioned by Correa et al. (*6*) to have a weaker association with passive smoking. The effect of passive smoking by cell type of lung cancer needs to be investigated further in studies with much larger numbers of nonsmokers.

Childhood lung disease may have a role in lung cancer etiology. Certain features of the lung of a child (e.g., susceptibility to airway closure and high peripheral resistance) might make it more vulnerable to residual abnormalities from respiratory illness (*26*). This notion is supported by observations that both smokers and nonsmokers with childhood respiratory diseases have impaired lung function capacity, that their rate of decline in ventilatory function capacity with age is more rapid than that in individuals without childhood respiratory problems, and that they have higher rates of clinical diagnosis of chronic obstructive pulmonary disease (*27, 28*). Women with childhood respiratory problems may have incurred epithelial damage to the airway resulting in airway hyperreactivity and are more susceptible to other insults to the lung. We cannot rule out the possibility of a chance finding or of preferential recall of childhood pneumonia by cases. However, our data appear to be internally consistent, since we found a significantly higher frequency of lung scarring mentioned in the pathology reports among cases with previous childhood pneumonia (12/30=40%) compared to those without (39/189=21%).

The association of lung cancer risk with exposure to coal heating or cooking warrants further investigation. Although coal was identified as the major heating or cooking fuel used during childhood and teenage years of a significantly higher proportion of cases, we did not have detailed information on the years of use. Excess risks of lung cancer have been reported for coke oven workers (*29, 30*) and British gas workers (*31*) who were heavily exposed to products of coal carbonization.

Studies of men suggest that their lung cancer risk is lowered by greater dietary β-carotene (*12-14, 32, 33*) and vitamin A intake (*15, 17, 32, 33*), but the evidence for women is less clear (*12, 13, 32, 33*). We observed a significantly increased risk for ADC with the lowest level of β-carotene consumption and a similar association for SCC. These results are consistent with findings for females in Singapore (*12*) and in Japan (*13*), but they are not supportive of data for females in Hawaii (*32*) and England (*33*). Our observation of no association with an index of total preformed vitamin A (i.e., dairy products, eggs, liver, and vitamin supplements) and no association with total vitamin A intake (preformed vitamin A and β-carotene—data not shown due to domination by preformed vitamin A) is consistent with findings for females in Hawaii (*32*). Conflicting findings have been reported for subgroups of preformed vitamin A foods and supplements. A higher consumption of liver and vitamin supplements has been reported previously for female cases as compared to controls, but the opposite result have been observed for males (*33, 34*). Our data show no case-control difference in the intake pattern of vitamin supplements and a higher consumption of liver among cases. Our finding of an elevated lung cancer risk associated with low levels of intake of dairy products has not been reported for females, although similar results have been observed for males (*15-17*). Our results on the role of β-carotene and preformed vitamin A were similar for ADC and SCC, despite suggestions that vitamin A (or β-carotene) is more strongly protective against SCC than against ADC (*17*).

Initial reports of an inverse relationship between blood retinol levels and subsequent risk of cancer at all sites (*35, 36*) have not been supported by recent studies (*37, 38*). This situation emphasizes the need to reexamine even the consistently observed association of vitamin A (or β-carotene) intake with male lung cancer.

Possible sources of bias in our data must be considered. Both lung cancer cases and controls were derived from population-based samples. However, because this disease is debilitating and rapidly fatal, 190 patients had died or were too ill to participate by the time of initial contact. We did not conduct proxy interviews because questions on childhood exposures and dietary history could not be assessed adequately. As expected, the group who was not

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interviewed was more likely to have metastatic disease at diagnosis but was similar in all demographic variables measured. In addition, information abstracted from medical records showed similar smoking status for those interviewed and those not interviewed. If cases who were not interviewed because of poor survival differed from those who survived longer and were interviewed in terms of the other risk factors under study, this could have biased our results. However, this appears unlikely since our data showed that histories of childhood pneumonia and exposure to coal fires were similar among cases regardless of stage of disease at diagnosis. There is also no evidence that cancer survival is associated with dietary vitamin A intake.

The etiology of SCC can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the ADC cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of ADC cases. Passive smoking and vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

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Akiba, S., Kato, H. and Blot, W.J., "Passive Smoking and Lung Cancer Among Japanese Women," Cancer Research 46: 4804-4807, 1986.

This case-control study involved female atom-bomb survivors in Hiroshima and Nagasaki, Japan (428 cases, 957 controls). Controls were matched on year of birth, city of residence, sex, participation in scheduled medical examinations, and vital status (including year of death). In excess of 90% of all interviews were with proxy respondents for both cases and controls. Only 57% of the cases were verified by pathological methods.

Questions were asked about exposure to ETS from spouse and parents. The authors reported an OR for female nonsmokers married to smokers of 1.5 (90% CI 1.0-2.5). They also claimed that risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease following cessation of exposure. Although no OR was presented, the authors wrote that no increased risk was associated with exposure to parental smoking during childhood.

The authors claimed that they were "unable to identify any strong confounding factors," including radiation exposure.

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[CANCER RESEARCH 46, 4804–4807, September 1986]

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Passive Smoking and Lung Cancer among Japanese Women

Suminori Akiba,[1] Hiroo Kato, and William J. Blot[1]

Radiation Effects Research Foundation, Hiroshima, Japan [S. A., H. K.], and National Cancer Institute, Bethesda, Maryland 20892 [W. J. B.]

ABSTRACT

A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers.

INTRODUCTION

As part of a case-control investigation of lung cancer among atomic bomb survivors conducted primarily to evaluate the interactive roles of cigarette smoking and ionizing radiation (1), data were collected on the smoking habits of the subject's spouses and parents. Herein we report the effect of exposure to such passive smoking, focusing on married women who had never smoked themselves.

MATERIALS AND METHODS

Since 1951 a cohort of 110,000 Hiroshima and Nagasaki atomic bomb survivors has been followed by the RERF,[2] formerly called the Atomic Bomb Casualty Commission (2). During the period 1971 to 1980, 525 newly diagnosed cases of primary lung cancer (Eighth Revision ICD 162.1) were identified among cohort members. The cases were ascertained from the Hiroshima and Nagasaki Tumor and Tissue Registries, the RERF mortality, surgical, and autopsy files, and Hiroshima University medical records. The diagnosis was based on biopsy or surgical pathology findings for 25%, on autopsy findings for 28%, on cytology for 4%, and on radiological/clinical findings for the remaining 43%. Since the cohort represents a fixed population that is aging over time and is older than the general population, the ages at diagnosis were higher than usual for lung cancer in Japan: the means were 72.1 for males and 70.2 for females; the ranges were 36 to 94 for males and 35 to 95 for females.

Controls were selected from among cohort members without lung cancer, 2 for each case in Hiroshima and 3 for each case in Nagasaki. The controls were individually matched to the cases with respect to yr of birth (± 2 yr), city of residence (Hiroshima or Nagasaki), sex, and whether or not they were among the 20% of the cohort participating in the program of biennial medical examinations given at RERF. In addition, controls were matched to cases on vital status. Since most of the cases had died, most of the controls were also deceased. The deceased controls were chosen according to the above-mentioned matching criteria, plus year of death (± 3 yr), and they were selected from among all causes of death except cancer and chronic respiratory disease. The distribution of the controls series is as follows: alive, 13%; deceased from cerebrovascular disease, 26%; from coronary heart disease, 13%; from other circulatory disease, 12%; from acute respiratory disease, 9%; from digestive disease, 8%; from accidents, 6%; and from other causes, 14%.

Interviews were sought during 1982 with all cases and controls, or their next of kin, who lived in Hiroshima and Nagasaki. The interviewers were aware that the study concerned lung cancer, but they were not told of the case-control status of the study subjects. A structured questionnaire was used to obtain histories of cigarette smoking and demographic, medical, occupational and other factors. If the individual was married, inquiry was made about the smoking status of the spouse, including the average number of cigarettes smoked per day, age started smoking, and, for those who stopped, the age of cessation of smoking. Using this information, together with the numbers of yr the husband and wife lived together, an index of exposure to the spouse's smoking was calculated. In addition, a single question was asked regarding whether the subject's mother and/or father smoked when the subject was living at home as a child.

OR were calculated as measures of the association between lung cancer and passive smoking and other factors (3). Estimates of the OR, and corresponding significance tests, were obtained by a conditional logistic regression analysis for matched data (4). Tests for trend used consecutive integers for levels of the ordered categories. Because there were *a priori* hypotheses that passive smoking might increase lung cancer risk, all significance tests for passive smoking effects were one-sided, with 90% CI used for interval estimates of the OR. Because interest focused on spouse smoking patterns, eliminated from the analyses were the one case and 6 controls among males and the 4 cases and 7 controls among females who were never married. Among the married individuals, almost all had been married to only one spouse. Among those with more than one spouse, information was available only for the most recent. Also excluded from each table were individuals with missing data for the variable being studied.

RESULTS

Interviews were obtained for 428 cases and 957 controls, respectively, 81% and 82% of the eligible cases and controls. The two primary reasons for nonresponse were the refusal of next of kin to answer questions about their deceased relatives and the decision not to attempt to locate next of kin for subjects who had moved out of Hiroshima or Nagasaki. The distribution of informants is given in Table 1, indicating that the information for most of the subjects was provided by next of kin. The type of respondent, however, was similar for cases and controls.

Table 2 shows the lung cancer OR according to the smoking status (smoker *versus* never smoked) of the subjects and their spouses. In both sexes there was an increased lung cancer risk associated with direct smoking. As indicated, almost all (93%) of the male lung cancer cases were smokers, but only a minority (38%) of the women with lung cancer in this population were reported to have ever smoked. Although not shown, the OR increased with the numbers of cigarettes usually smoked per day during adulthood for both men and women. Among males who smoked 1 to 9, 10 to 19, 20 to 29, and 30+ cigarettes per day, the OR were 1.7, 1.8, 3.4, and 9.7, respectively (P for trend < 0.01). Among females who smoked 1 to 9, 10 to 19, and 20+ cigarettes per day, the OR were 1.9, 2.0, and 4.9 (P for trend < 0.01). Table 2 shows that among female nonsmokers married to smokers, there was an elevated risk for lung cancer (OR = 1.5; 90% CI = 1.0 to 2.5; $P = 0.07$). Although similar increases associated with smoking habits of spouses were observed for female smokers and for male nonsmokers and smokers, suffi-

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[1] To whom requests for reprints and correspondence from outside the United States should be addressed, at Department of Epidemiology and Statistics, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Hiroshima 730, Japan (S. A.), and from the United States, at Epidemiology and Biostatistics Program, National Cancer Institute, Landow Building 3C16, Bethesda, MD 20892 (W. J. B.).

[2] The abbreviations used are: RERF, Radiation Effects Research Foundation; OR, odds ratio(s); CI, confidence interval(s).

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Table 1 *Percentage distribution of respondents*

	Sex of study subject (%)			
	Male		Female	
Respondent	Case	Control	Case	Control
Self	6	7	16	19
Spouse	51	48	12	11
Child	23	22	33	33
Daughter-in-law	11	12	18	17
Others	10	10	21	19
Total %	100	100	100	100
n	264	595	164	362

Table 2 *Odds ratios for lung cancer according to smoking status of the subject and his/her spouse*

Sex of subject	Subject smoker	Spouse smoker	Case	Control	OR[a]	90% CI[a]
Male	No[b]	No[b]	16	101	1.0[c]	
		Yes	3	9	1.8	(0.5, 5.6)
	Yes	No	190	388	3.4	(2.1, 5.5)
		Yes	51	86	4.2	(2.4, 7.3)
Female	No[b]	No[b]	21	82	1.0[c]	
		Yes	73	188	1.5	(1.0, 2.5)
	Yes	No	8	14	2.2	(0.9, 5.1)
		Yes	50	56	3.6	(2.1, 6.1)

[a] Odds ratio and 90% CI from matched analysis.
[b] Individual reported never to have smoked cigarettes.
[c] Referent category.

Table 3 *Odds ratios for lung cancer among nonsmoking women according to husband's usual daily consumption of cigarettes*

No. of cigarettes husband usually smoked/day	Case	Control	OR[a]	90% CI[a]
0	21	82	1.0	
1–19	29	90	1.3	(0.7, 2.3)
20–29	22	54	1.5	(0.8, 2.8)
30+	12	23	2.1	(0.7, 2.5)
			(*P* for trend = 0.06)	

[a] Odds ratio and 90% CI from matched analysis.

Table 4 *Odds ratios for lung cancer among nonsmoking women according to husband's duration of smoking cigarettes while married*

Yr husband smoked cigarettes	Case	Control	OR[a]	90% CI[a]
0	21	82	1.0	
1–19	20	30	2.1	(1.0, 4.3)
20–39	29	81	1.5	(0.8, 2.7)
40+	22	59	1.3	(0.7, 2.5)

[a] Odds ratio and 90% CI from matched analysis.

cient data for detailed analyses of passive smoking patterns were available only for female nonsmokers.

The data for nonsmoking women are categorized in Table 3 according to the number of cigarettes the husband usually smoked per day during adulthood. There was an increasing lung cancer risk with increasing amount smoked per day by the husband, with the OR slightly exceeding 2-fold for women whose husbands were heavy smokers. No monotone trend of increasing risk associated with increasing duration of exposure to husband's smoking was found (Table 4). Risks according to time of exposure are examined in Table 5. The odds ratios were lower among "ex-passive smokers" than among women who had been exposed to their husbands' smoking within the past 10 yr. The reduction in risk with cessation of exposure remained after adjusting for the amount of cigarettes smoked per day by the spouse.

Table 5 *Odds ratios for lung cancer among nonsmoking women according to recency of exposure to husbands' smoking*

Time of exposure	Case	Control	OR[a]	90% CI[a]
None	21	82	1.0	
Not exposed within last 10 yr[b]	31	87	1.3	(0.9, 2.4)
Exposed within last 10 yr	40	85	1.8	(1.0, 3.2)
			(*P* for trend = 0.05)	

[a] Odds ratio and 90% CI from matched analysis.
[b] These "ex-passive smokers" are those whose husbands quit smoking 10 or more yr prior to the diagnosis of lung cancer (or 10 or more yr prior to the date of selection for controls) or those who were not living with their husbands because of separations, divorce, or his death 10 or more yr prior to the diagnosis.

Table 6 *Odds ratios of lung cancer among nonsmoking women according to their occupation and their husbands' smoking status*

Occupation of subject	Husband's smoking status[a]	Case	Control	OR[b]	90% CI[b]
Housewife[c]	Never	6	20	1.0[d]	
	Light	11	34	0.9	(0.4, 2.1)
	Heavy	15	35	1.5	(0.7, 3.3)
White collar[e]	Never	7	23	1.0	(0.4, 2.4)
	Light	9	20	1.7	(0.7, 4.5)
	Heavy	8	16	1.6	(0.6, 4.1)
Blue collar[f]	Never	6	21	1.1	(0.4, 2.9)
	Light	5	22	0.5	(0.2, 1.5)
	Heavy	7	6	10.4	(1.6, 66.7)

[a] Light, husband smoked less than 20 cigarettes/day; heavy, husband smoked 20 or more cigarettes/day.
[b] Odds ratio and 90% CI from matched analysis.
[c] Housewife defined as woman who was employed outside the home for no more than 10 yr.
[d] Reference category.
[e] Office and sales workers.
[f] Excludes 5 cases and 34 controls who were farmers.

As shown in Table 6, the risk of lung cancer tended to increase in relation to exposure to the husband's tobacco smoke for each of housewives, white collar, and blue collar workers. The highest odds ratio occurred for women who had blue collar jobs and were married to men who smoked one or more packs of cigarettes per day, but the numbers involved were small.

The odds ratios from the matched logistic regression analyses presented in Tables 2 to 6 are generally similar to unadjusted odds ratios that can be calculated from the cross-products of the numbers of exposed and unexposed cases and controls, indicating that confounding in unadjusted analyses by age, city, vital status, and yr of death (the matching factors) is not substantial. We also assessed whether the associations with passive smoking were consistent across the various strata defined by the matching factors. The numbers of subjects in several of the categories became quite small with this fine a cross-classification, but the trends with husbands' smoking tended to be seen throughout, with no strong differences by age group or by city of residence. The trends were also apparent for each type of informant (self, husband, child, and other); in particular the elevated risk for heavy relative to nonexposure to husbands' smoking was detected when data were reported by the husbands or subjects themselves. Radiation exposure was also examined as a potential confounder and effect modifier. No significant influence of radiation dose on the passive smoking association was detected, although the trends with passive smoking seemed stronger among the unexposed.

Information on the histological types of lung cancer was unavailable for 43% of the cases who were diagnosed only on radiological or clinical evidence. We conducted separate analyses among those with and without a pathological confirmation of lung cancer and found increased risks associated with passive smoking for both groups. The OR among nonsmoking women

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married to smokers was 1.4 for the cases and their matched controls with a histologically confirmed diagnosis, and 1.6 for those with a clinical/radiological diagnosis. Among women with a histological diagnosis, adenocarcinoma was the predominant cell type, but the distribution of histological types varied by smoking status (Table 7). The percentage of squamous and small cell carcinoma was much higher among smokers than nonsmokers. Although based on small numbers, there were also more squamous and small cell cancers among nonsmoking females whose husbands smoked.

Responses to the question on parental smoking while the subject was a child were provided for only two-thirds of the subjects. Among these the mothers of the subjects were reported to be smokers for 13% of the cases and 17% of the controls, and the fathers, for 67% of the cases and 66% of the controls. Hence there was no overall increased risk associated with parental smoking, nor was there any significant increase after stratifying by smoking status of the subject. Among male smokers, the OR for lung cancer associated with maternal smoking was 1.1.

DISCUSSION

The results from this case-control study suggest that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratios for lung cancer among nonsmoking women tended to increase with amount smoked by their husbands, a trend seen among housewives as well as women who worked outside the home. The highest odds ratios among nonsmokers were for women who worked in blue collar jobs whose husbands were heavy smokers, women presumably with the highest exposure to environmental tobacco smoke. There was little association with parental smoking or with ex-passive smoking, suggesting that cessation of exposure may lower risk.

The findings are generally consistent with results of a national cohort study of mortality among Japanese women (5) and of several epidemiological investigations conducted elsewhere in the world (6–8). Updated follow-up for the period 1966 to 1981 of the study conducted among an adult population selected from multiple areas throughout Japan, excluding Hiroshima and Nagasaki, showed a gradient in mortality with amount smoked by the husband (9). The increase in risk reached 90% among those whose husbands smoked 20 or more cigarettes per day, a figure in line with the 2-fold excess for 30 or more cigarettes per day of smokers in our study. The similarity in results, despite different methodological approaches, suggests that the association between lung cancer and passive smoking is not an artifact of recall bias which can affect retrospective studies. Furthermore, we were unable to identify any strong confounding factors, including radiation exposure, that may have accounted for the passive smoking association.

It is noteworthy that a recent survey in Kyoto, Japan, found significantly elevated levels of cotinine, the major metabolite of nicotine, in the early morning urine of nonsmokers who lived in households with smokers or worked in offices/factories with smokers (10). The cotinine concentrations among nonsmokers living with 2-pack-a-day smokers were roughly equivalent to the cotinine levels of smokers of less than 3 cigarettes per day. Precise estimates of the lung cancer risk associated with this level of smoking are not available, since not many smoke so few cigarettes per day. However, 3 well-known prospective studies of mortality among smokers [the American Cancer Society study involving nearly 1 million volunteers (11), the 16-yr follow-up of 250,000 United States veterans (12), and the 20-yr follow-up of 34,000 British doctors (13)] found relative risks of lung cancer of 4.6, 4.8, and 7.8 among 1 to 9, 1 to 9, and 1 to 14 cigarette-per-day smokers, respectively. Linear interpolation between these values and the base-line level of 1.0 for nonsmokers would yield estimated relative risks for 1 to 2 cigarette-per-day smokers of nearly 2-fold, about the same order of increase observed for "heavy" passive smokers in this study. Hence, if the Kyoto results (10) are applicable elsewhere,[3] and if urinary cotinine levels reflect levels of exposure to the carcinogenic substances in tobacco smoke, then the observed magnitude of the increased lung cancer risk among passive smokers in Japan seems not greatly out of line with what might be expected based on their exposure to environmental tobacco smoke.

It should be noted that the risk ratios for lung cancer associated with direct smoking (as shown in Table 2) were lower in this case-control study than typically found in case-control and cohort investigations in other countries (14). The lower OR among smokers in part arises from our selection, in order to minimize respondent bias, of controls matched to cases on vital status, which led to the inclusion of some controls who died of smoking-related diseases. However, lung cancer risk ratios generally similar to those in this study were also reported in the prospective study of Japanese adults (9). Because of the lower relative risks of lung cancer among smokers in Japan, differences in the OR between direct and passive smokers are not as high as in western countries. Indeed, we found OR for "heavy" passive smokers to be nearly equal those for women who were reported to be light smokers themselves. While such similarity was unexpected, characteristics such as the size and style of residential units might result in a higher environmental-to-direct tobacco smoke exposure ratio in Japan (and thus less of a difference in OR for lung cancer between passive and direct smokers). This in fact is suggested by the comparison of the cotinine analyses between Japan and Great Britain (10, 15), where the ratio of cotinine levels in passive compared to direct smokers was considerably higher in Japan. Our finding that lung cancer risk among nonsmokers may be less closely related to duration of exposure to tobacco smoke, the major determinant of lung cancer risk among smokers (13), than to intensity and recency of exposure also may be noteworthy. Such a difference might contribute to a higher ratio in Japan of lung cancer risks in passive compared to direct smokers, since the current prevalence of smoking is higher in Japan than in either Great Britain or the United States, but the marked temporal increase in smoking began later (9, 16).

The present study did not replicate the finding of a case-control study in Louisiana which showed a higher risk among male smokers whose mothers had smoked (7). Although we did find higher percentages of smokers among both cases and controls and among both men and women whose parents had been smokers, there was no elevation in the OR among smoking

Table 7 *Percentage histological distribution of lung cancers among females according to their and their husbands' smoking status*

Subject smoker	Husband smoker	Cell type (%)	
		Squamous or small cell cancer	Adenocarcinoma or large cell cancer
No	No	0	100
	Yes	16	84
Yes		58	42

[3] There is some question about their generalizability, since cotinine levels among heavy passive smokers in Kyoto were about one-seventh the levels in average smokers, in contrast to about one-fiftieth in a recent British study (15). In both studies, however, the urinary levels increased in proportion to estimated passive smoking exposure.

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Japanese men or women associated with maternal or paternal smoking. However, it was often difficult for the respondents to provide information on parental smoking, and data on this exposure were missing for about one-third of the subjects.

One of the concerns in this study was the adequacy of data provided by surrogate respondents. Only a minority of the patients could be interviewed directly because of the often fatal outcome of lung cancer and the need to include cases diagnosed as early as 1971 in order to assemble sufficient numbers of subjects for analysis. The distribution of respondent types was comparable between cases and controls so that response bias is unlikely, but the possibility of poor quality information for both cases and controls existed. We could evaluate this possibility, however, since many of the cases and controls had provided information on their smoking habits in routine RERF surveys conducted in the 1960s when all study subjects were alive (1, 2). The data in Table 8 indicate very high concordance in the identification of a female as a nonsmoker or smoker by a next of kin in 1982 and by the woman herself in the 1960s. In addition to providing some confidence that the data provided by surrogates are adequate, the confirmation of nonsmoking status by a next of kin argues against the possibility that Japanese women tend to report themselves as nonsmokers when they actually smoke. The 1982 survey revealed a higher percentage of male smokers than reported earlier, but the increase was both for self as well as next-of-kin interviews and may reflect an actual increase in smoking prevalence over time. Questions about the smoking habits of spouses were not asked in the surveys in the 1960s, so that self *versus* surrogate reporting on this variable cannot be assessed directly. In our study, however, there were no significant differences in the passive smoking trends according to respondent type. In particular, an increased OR was seen for nonsmoking women whose husbands were heavy smokers when the data were reported by the husbands themselves.

Another concern in this case-control study was the reliability of the diagnoses of lung cancer. Forty-three % of the cases were diagnosed solely on clinical and/or radiological evidence. The percentage was high in large part because the cohort being followed was elderly, and surgical or biopsy procedures were less likely to be performed on older patients. The OR associated with passive smoking, however, were similar when calculations were restricted to histologically confirmed cases. We also calculated OR after deleting 23 cases and their matched controls for whom a diagnosis of possible or probable lung cancer was made only on radiological grounds and who had survived 5 or more yr (all were in fact living as of January 1984), since the diagnoses for at least some appear to be questionable. Little change was noted. Smoking has been shown to induce all types of lung cancer, but its effect is greater for squamous and small cell carcinoma than adenocarcinoma (17). Whether passive smoking might have the same predilection for squamous cancers is not clear, but our limited histological data (Table 7) are consistent with this notion. It is of interest that the highest OR for passive smoking has been reported from a case-control study in Greece (6, 18, 19) where the cases were limited to lung cancers other than adenocarcinoma.

Table 8 *Comparison of smoking status from the 1982 case-control study and RERF surveys in 1964 to 1968*

The numbers of paired responses for the 4 sex-informant categories below are 58, 679, 45, and 92, respectively.

Sex of subject	Informant in 1982	1964–1968 current smoker	1982 smoking status (%)	
			Never	Smoker
Male	Self	No	18	14
		Yes	0	68
	Surrogate	No	12	13
		Yes	1	74
Female	Self	No	87	0
		Yes	0	13
	Surrogate	No	65	3
		Yes	0	32

In summary, the results of this investigation suggest that exposure to environmental tobacco smoke may increase the risk of lung cancer among nonsmokers. The findings, from one of the two areas of the world where the possibility of a passive smoking hazard was first postulated, add to an accumulating body of evidence on the issue. While the total evidence is not definitive and not all studies show significantly positive associations (20–22), the results are suggestive enough to warrant further evaluation in larger studies where passive smoking exposures can be more fully quantified.

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Lee, P.N., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.

As a subset of a large hospital-based case-control study of lung cancer, chronic bronchitis, ischaemic heart disease and stroke, some individuals were asked questions about "passive smoking." Of a total of 3,832 cases and controls, 47 cases (15 male, 32 female, all lifelong nonsmokers) and 96 controls (30 male and 66 female) were included in the ETS analysis.

RRs for spousal smoking were calculated as follows: for males, RR = 1.30 (95% CI 0.38-4.39), and for females, RR = 1.00 (95% CI 0.37-2.71). Seven indices of ETS exposure were also examined: exposure at home, at work, during travel, during leisure, a combination of the above four indices, spousal smoking in the last 12 months, and spousal smoking at any time during the marriage. No statistically significantly elevated risks were reported.

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Br. J. Cancer (1986), 54, 97–105

Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases

P.N. Lee,* J. Chamberlain & M.R. Aldersont

Institute of Cancer Research, Clifton Road, Belmont, Surrey, UK.

Summary In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischaemic heart disease or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all.

Study of hospital in-patients

In 1977 a large hospital case-control was initiated to study the relationship of the type of cigarette smoked to risk of lung cancer, chronic bronchitis, ischaemic heart disease and stroke. This study was carried out in 10 hospital regions in England; interviewing ended in January 1982. The original questionnaire did not include questions on passive smoking as it was not considered an important issue in 1977. However, in 1979 it was decided to extend the questionnaire to cover passive smoking for married patients for the last four regions to begin interviewing. Subsequently, in 1981, following publication of the papers by Hirayama (1981) and by Trichopoulos *et al.* (1981) claiming that non-smoking wives of smokers had a significantly greater risk of lung cancer than non-smoking wives of non-smokers, it was decided to increase the number of interviews of married lung cancer cases and controls. The extended questionnaire was then administered to these patients in all hospitals where interviewing was still continuing.

Follow-up study of spouses of non-smoking hospital in-patients

In 1982, after interviewing of hospital in-patients had been completed, it was decided to carry out a follow-up study. In this study, an attempt was made to interview the spouses of all of the married hospital in-patients with lung cancer who reported never having smoked, as well as of two married non-smoking controls for each of these index lung cancer cases. The follow-up study was intended partly to compare information on spouses' smoking habits obtained first-hand with that obtained second-hand during the in-patient interviews, and partly to obtain some data on spouses' smoking habits for those patients who had not answered passive smoking questions in hospital.

This paper concentrates solely on the issue of passive smoking in lifelong non-smokers. Results relating to type of cigarette smoked are described elsewhere (Alderson *et al.*, 1985), while a detailed report, available on request from PNL, considers the overall findings from this case-control study.

Methods and response

Study of hospital in-patients

For each of the 4 index diagnoses (lung cancer, chronic bronchitis, ischaemic heart disease and stroke), the intention was to interview 200 cases and 200 matched controls in each of the eight sex/age cells (i.e. male or female, and aged 35–44, 45–54, 55–64 or 65–74). This gave a target of 12,800 patients, though for some categories (e.g. young female chronic bronchitics) this would be unattainable. Patients were selected from medical (including chest medicine), thoracic surgery, and radiotherapy wards. Controls were patients without one of the four index diagnoses, individually matched to cases on sex, age, hospital region and,

Correspondence: P.N. Lee.
*Present address: 25 Cedar Road, Sutton, Surrey, SM2 5DG.
†Present address: Office of Population Censuses and Surveys, St. Catherine's House, 10 Kingsway, London WC2B 6JP.

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when possible, hospital ward and time of interview. Subsequently, when final discharge diagnoses became available, they were used to reallocate cases and controls as necessary. Patients without a final diagnosis kept their provisional diagnosis. Where changes in case-control status occurred, patients were regrouped into new case-control pairs as appropriate. With the assistance of Sir Richard Doll and Mr Richard Peto, non-index diagnoses were classified as follows:

class 1A 'definitely not smoking associated'
class 1B 'probably not smoking associated'
class 2A 'probably smoking associated'
class 2B 'definitely smoking associated'

Controls with no final diagnosis were considered class 1B. Overall, there were 12,693 interviews carried out which resulted in 4,950 pairs with class 1 controls and 720 pairs with class 2 controls.

There were 3,832 interviews of married cases and controls where the passive smoking questionnaire was completed. In order to avoid substantial loss of data, due to one member of a pair not being married or not completing the passive smoking questionnaire, it was decided to ignore matching when analysing the passive smoking data and to compare each index group with the combined controls. Numbers by sex and case-control status are given in Table 1.

Table 1 Numbers of married hospital in-patients completing passive smoking questionnaires

	Male	Female	Total
Lung cancer	547	245	792
Chronic bronchitis	182	84	266
Ischaemic heart disease	286	221	507
Stroke	161	137	298
Controls			
Class 1A and 1B*	839	713	1,552
Class 2A and 2B*	268	149	417
Total	2,283	1,549	3,832

*Other diseases were classified by degree of smoking association - class 1A: definitely not, class 1B: probably not, class 2A: probably, class 2B definitely.

In the passive smoking part of the questionnaire, patients were asked when the marriage started, if and when it had ended; the number of manufactured cigarettes per day smoked by the spouse both during the last 12 months of marriage and also at the period of maximum smoking during the marriage; and whether the spouse ever regularly smoked hand-rolled cigarettes, cigars or a pipe during the marriage. For second or subsequent marriages, questions related to the first marriage to give the longest latent interval between exposure and disease onset. The patients were also asked to quantify, according to a four-point scale (a lot, average, a little, not at all), the extent to which they were regularly exposed to tobacco smoke from other people prior to coming into hospital in 4 situations: at home; at work; during daily travel; during leisure time. In the main questionnaire, detailed questions were asked on smoking habits and on a whole range of possible confounding variables.

Follow-up study of spouses of non-smoking hospital in-patients

From the hospital study there were 56 lung cancer cases who reported being lifelong non-smokers, who were married at the time of interview and who were not known to have been married previously. In a follow-up to the main study, an attempt was made to interview the spouses of these 56 cases and also the spouses of two life-long non-smoking controls for each case, individually matched for sex, marital status and 10-year age group and, as far as possible, hospital. Where multiple potential controls in the same hospital were available, those interviewed nearest in time to the case were selected. Where suitable controls in the same hospital were not available, those in the nearest hospital were chosen.

Because names and addresses of the patients were not recorded in the hospital study, it was necessary to go back to the hospital both to obtain this information and also to get permission to interview their spouses. Following some refusals both by the hospital and by the spouses, successful interviews were obtained from spouses of 34 cases (10 wives and 24 husbands) and 80 controls (26 wives and 54 husbands) whose condition was definitely or probably not related to smoking.

Interviewing was carried out between July 1982 and August 1983. The spouses were asked about their consumption of manufactured cigarettes, cigars and pipes (a) nowadays, (b) during the year of admission of the patient or (c) maximum during the whole of the marriage. The spouses were not asked about the smoking habits of the index patient. The spouses were also asked questions on age, occupation, social class and a range of other potential confounding factors.

Statistical methods

The statistical methods are based on classical procedures for analysis of grouped data derived from case-control studies (Breslow & Day, 1980). In general, the material has been examined as a $2 \times K \times 5$ table, with K representing the levels of the

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risk factor of interest and S the number of strata used to take account of potential confounders.

Results presented are for the combined strata and show the relative risk (Mantel-Haenszel estimate) together with the significance of its difference from a base level (risk 1.0), and/or the dose-related trend. In analyses of the data collected in hospital, comparisons are made between cases with a particular index disease and all the controls with diseases definitely or probably not related to smoking. Six simple indices of passive smoke exposure were considered in these latter analyses, (i)–(iv) exposure at home, at work, during travel, during leisure, (v) spouse smoking manufactured cigarettes in the last 12 months, and (vi) spouse smoking manufactured cigarettes in the whole of the marriage. Bases for (ii) are reduced as not all patients worked. In addition, a combined index of passive smoke exposure was calculated by the unweighted sum of the four individual exposure indices (i)–(iv), counting 'not at all' as 0, 'little' as 1, 'average' as 2 and 'a lot' as 3.

Results

Lung cancer

The follow-up study concerned 56 lung cancer cases and 112 matched controls who reported never having smoked in their hospital interview. Of these, there were 47 cases (15 male and 32 female) and 96 controls (30 male and 66 female) for whom some information on smoking habits of their spouses was available. Of these 143 patients, information on spouse smoking was available both from the spouse and from the patient for 59 (41%), from the spouse only for 55 (38%) and from the patient only for 29 (20%). Table II shows the estimated age-adjusted relative risk of lung cancer in relation to spouse smoking during the whole of the marriage, by sex, source of data, and period of smoking. None of the 9 relative risks shown in the table are statistically significant. When data for both sexes and both sources are considered, the estimated relative risks in relation to spouse smoking are close to 1 (1.11). For individual sexes or sources, where numbers of cases and controls are smaller, relative risks vary more from unity, but no consistent pattern is evident. Similar conclusions were reached, when analyses were based on smoking during the year of hospital interview. Here, the overall relative risk was again close to 1 (0.93 with limits 0.41–2.09).

Table III summarises concordance between spouse's manufactured cigarette smoking habits as reported directly and indirectly for the 59 patients with data from both sources. Discrepancies were seen for 9 spouses (15%) in respect of smoking at some time during marriage and in the case of 2

Table II Relationship between spouse's manufactured cigarette smoking during the whole of the marriage and risk of lung cancer among lifelong non-smokers (standardised for age)

Sex of patient	*Spouse did not smoke*		*Spouse smoked*		*Relative risk (95% limits)*
	Cases	*Controls*[a]	*Cases*	*Controls*[a]	
Based on interviews of the spouse in follow-up study (114 patients)					
Male	5	13	5	13	1.01(0.23–4.41)
Female	5	16	19	38	1.60(0.44–5.78)
Combined	10	29	24	51	1.33(0.50–3.48)
Based on interviews of the index patient in hospital (88 patients)					
Male	7	15	5	7	1.53(0.37–6.34)
Female	9	17	8	20	0.75(0.24–2.40)
Combined	16	32	13	27	1.00(0.41–2.44)
Based on both sources of information (143 patients)[b]					
Male	7	16	8	14	1.30(0.38–4.39)
Female	10	21	22	45	1.00(0.37–2.71)
Combined	17	37	30	59	1.11(0.51–2.39)

[a]Only controls included in follow-up study considered. [b]In this analysis the spouse was counted as a smoker if reported to be so either directly, by the spouse during follow-up interview, or, indirectly, by the patient in hospital. Note that the 59 patients for whom information on spouse smoking was available from both sources are included in all 3 analyses.

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Table III Concordance between spouse's manufactured cigarette smoking habits as reported directly and indirectly

	Sex of patient/case control status				
	Male		Female		
	Cases	Controls	Cases	Controls	Total
Spouse a smoker sometime in marriage according to					
Subject and spouse	2	6	5	13	26
Only subject	1	0	0	3	4
Only spouse	1	1	3	0	5
Neither	3	11	1	9	24
% subject/spouse agreement	71%	94%	67%	88%	85%
Spouse a smoker during year of hospital interview according to					
Subject and spouse	1	6	2	4	13
Only subject	0	0	0	1	1
Only spouse	1	0	0	0	1
Neither	5	12	7	20	44
% subject/spouse agreement 86%	86%	100%	100%	96%	97%

spouses (3%) in respect of smoking during the year of hospital interview. There was no consistent pattern in the direction of discrepancy.

Table IV summarises the results of analyses carried out relating 7 indices of passive smoke exposure recorded in the hospital interviews to risk of lung cancer among lifelong non-smokers. Here the controls used for comparison are all never smoking patients with diseases classified as definitely or probably not associated with smoking who completed the passive smoking questionnaire.

Overall the results showed no evidence of an effect of passive smoking on lung cancer incidence among lifelong non-smokers. In male patients, relative risks were increased for some of the indices but numbers of cases were small and none of the differences approached statistical significance. In females, where numbers of cases were larger, such trends as existed tended to be negative and indeed were marginally significantly negative ($P < 0.05$) for passive smoking during travel and during leisure. For the combined sexes no differences or trends were statistically significant at the 95% confidence level; such trends as existed tending to be slightly negative. The relative risk in relation to the spouse smoking during the whole of the marriage was estimated to be 0.80 for the sexes combined, with 95% confidence limits of 0.43 to 1.50. Standardisation for working in a dusty job, the variable apart from smoking found to have the strongest association with lung cancer risk in the analyses described in Alderson *et al.* (1985), did not affect the conclusion that passive smoking was not associated with risk of lung cancer among never smokers in our study.

Chronic bronchitis, ischaemic heart disease and stroke

Analyses similar to that shown in Table IV for lung cancer were also carried out for chronic bronchitis, ischaemic heart disease and stroke. Illustrative results for two of the indices are presented in Table V.

No significant relationship of any index of passive smoking to risk of the 3 diseases was seen. For the sexes combined, the relative risk in relation to the spouse smoking during the whole of the marriage was 0.83 for chronic bronchitis (95% confidence limits 0.31–2.20), 1.03 for ischaemic heart disease (limits 0.65–1.62) and 0.90 for stroke (limits 0.53–1.52). For stroke there was, in both sexes, an approximate 2-fold increase in risk for patients with a combined passive smoke index that was high (score of 5 to 12) compared with those where it was low (score of 0 or 1). However, numbers of cases with a high score were low (14 males and 7 females) and even for the sexes combined, the relative risk estimate of 2.18 was not statistically significant (limits 0.86–5.48). In interpreting this finding, it should be noted that active smoking was not found to be clearly related to stroke in the main study (Alderson *et al.*, 1985), rendering a two-fold increase in relation to passive smoking *a priori* unlikely.

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Table IV. Relationship between various indices of passive smoke exposure and risk of lung cancer among lifelong non-smokers (standardised for age and, for spouse smoking, whether the marriage was ongoing or ended)

Passive smoke exposure index/level	*Male patients*			*Female patients*			*Sexes combined*		
	Cases	*Controls*	*R*	*Cases*	*Controls*	*R*	*Cases*	*Controls*	*R*
At home									
Not at all	9	101	1	21	192	1	30	293	1
Little	2	21	1.22	6	65	0.92	8	86	0.98
Average/a lot	1	11	1.11	5	61	0.81	6	72	0.86
At work									
Not at all	3	40	1	12	113	1	15	153	1
Little	6	29	3.24	3	26	1.18	9	55	1.82
Average/a lot	1	29	0.46	0	19	0.0	1	48	0.19
During travel									
Not at all	8	101	1	28	238	1	36	339	1
Little	3	16	2.06	2	51	0.33	5	67	0.64
Average/a lot	0	13	0.00	0	13	0.00	0	26	0.00
						Trend (negative) $P<0.05$			
During leisure									
Not at all	3	45	1	15	116	1	18	161	1
Little	4	48	1.12	14	107	1.05	18	155	1.06
Average/a lot	5	39	3.18	2	95	0.18	7	134	0.59
						Trend (negative) $P<0.05$			
Combined index*									
Score 0–1	1	27	1	10	75	1	11	102	1
Score 2–4	7	55	4.34	5	61	0.63	12	116	1.08
Score 5–12	2	15	3.20	0	21	0.00	2	36	0.50
Spouse smoked man cigs in last 12 months									
No	10	105	1	20	193	1	30	298	1
Yes	2	29	0.96	11	122	0.76	13	151	0.79
Spouse smoked man cigs in whole of marriage									
No	7	93	1	13	89	1	20	182	1
Yes	5	40	2.47	19	229	0.55	24	269	0.80

*Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for at home, at work, during travel, during leisure.

Discussion

Over the past 4 years there has been considerable research interest in the relationship between passive smoking and risk of lung cancer in nonsmokers. While some studies have claimed a positive effect (Hirayama, 1981; Trichopoulos *et al.*, 1981; Correa *et al.*, 1983; Garfinkel *et al.*, 1985, Gillis *et al.*, 1984, Knoth *et al.*, 1983), others (Buffler *et al.*, 1984, Chan, 1982; Garfinkel, 1981; Kabat and Wynder, 1984, Koo *et al.*, 1984) have found no significant relationship. Relative risks of lung cancer for non-smoking women married to smokers compared to non-smoking women married to non-smokers range from somewhat over 2 in the Trichopoulos and Correa studies to around 0.75 in the Buffler and Chan studies. The weighted relative risk from these studies has been estimated by us as approximately 1.3. While there is, therefore, a tendency for a small positive *association* between passive smoking and lung cancer, recent reviews of these data (Lee, 1984, Lehnert *et al.*, 1984) have concluded that overall there is no reliable scientific evidence of a causal relationship between passive smoking and lung cancer. In these reviews a number of general points have been made.

First, dosimetric studies have shown that, in cigarette-equivalent terms, passive smoking only results in a relatively small exposure to the non-smoker. Hugod *et al.* (1978), for example, showed that even under quite extreme conditions the time taken for a non-smoker to inhale the equivalent of

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Table V Relationship between two indices of passive smoke exposure and risk of chronic bronchitis, ischaemic heart disease and stroke among lifelong non-smokers (standardised for age and, for spouse smoking, whether the marriage was ongoing or ended)

Passive smoke exposure index/level	Male patients			Female patients			Sexes combined		
	Cases	Controls	R	Cases	Controls	R	Cases	Controls	R
Chronic bronchitis									
Combined index*									
Score 0–1	1	27	1	7	75	1	8	102	1
Score 2–4	2	55	0.83	4	61	1.05	6	116	1.00
Score 5–12	1	15	1.90	1	21	1.03	2	36	1.30
Spouse smoked man cigs. in whole of marriage									
No	8	93	1	4	89	1	12	182	1
Yes	1	40	0.34	13	229	1.22	14	269	0.83
Ischaemic heart disease									
Combined index*									
Score 0–1	15	27	1	23	75	1	38	102	1
Score 2–4	12	55	0.43	9	61	0.59	21	116	0.52
Score 5–12	3	15	0.43	4	21	0.81	7	36	0.61
Spouse smoked man cigs. in whole of marriage									
No	26	93	1	22	89	1	48	182	1
Yes	15	40	1.24	55	229	0.93	70	269	1.03
Stroke									
Combined index*									
Score 0–1	5	27	1	19	75	1	24	102	1
Score 2–4	10	55	1.24	10	61	0.86	20	116	0.97
Score 5–12	4	15	1.77	7	21	2.44	11	36	2.18
Spouse smoked man cigs. in whole of marriage									
No	18	93	1	19	89	1	37	182	1
Yes	6	40	0.84	49	229	0.92	55	269	0.90

*Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for at home, at work, during travel, during leisure.

one cigarette would be 11 hours as regards particulate matter and 50 hours as regards nicotine. Similarly, Jarvis *et al.* (1985) have shown that the increase in salivary cotinine in relation to passive smoke exposure is less than 1% of that in relation to active smoke exposure. Extrapolating linearly from the 10-fold relative risk of lung cancer in relation to active smoking would therefore predict a relative risk in relation to passive smoking less than 1.1, while a quadratic extrapolation, as suggested by Doll and Peto (1978) would predict a lower risk still. The conflict between the dose and the claimed response is particularly clear for the results of Hirayama (1981) who found a similar effect on lung cancer for passive smoking as for active smoking of 5 cigarettes a day.

Second, all the studies suffer from weak exposure data, most studies only obtaining information on the spouse's smoking habits and none obtaining objective data by measurement of ambient levels of smoke constituents in the air of the home or workplace and/or of concentrations of constituents in body fluids.

Third, no studies adequately take into account the possibility that misclassification of active smokers as non-smokers may have consistently biased relative risk estimates upward. Active smokers have a high relative risk of lung cancer and spouses' smoking habits are positively correlated. Because of this, it can be shown that if a relatively small proportion of smokers deny smoking, this results in an *apparent* elevation in risk of lung cancer in 'non-smokers' married to smokers compared to 'non-smokers' married to non-smokers, even when no *true* effect of passive smoking exists. A demonstration that this source of bias is of real importance can be found in the study of Garfinkel *et al.* (1985). Based on unvalidated smoking data taken from hospital notes, a relative risk of lung cancer in relation to husband's smoking at *home* of 1.66 was calculated, with relative risks of at least 1.3 seen in relation to each

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level of husband's cigarette smoking and in relation to husband's cigar and pipe smoking. When additional sources of information on smoking habits were used, the overall relative risk was reduced to a marginally significant 1.31 with an elevated risk only really discernible in relation to heavy cigarette smoking by the husband. Even here, it is notable that the elevation in risk was not evident when smoking data were obtained from the subject or her spouse directly, but was only evident when the data were obtained from the daughter or son or another informant, i.e. from those people who were less likely to have known the full smoking history. The lower relative risk may still have arisen wholly or partly as a bias resulting from misclassification of smoking habits.

Fourth, many of the studies are open to specific criticisms. For example, the conclusion of Gillis *et al.* (1984) that male lung cancer deaths in non-smokers rose from 4 per 10,000 in those not exposed to passive smoke to 13 per 10,000 in those who were exposed was based on a total of only 6(!) deaths and was not statistically significant. Also the claim by Knoth *et al.* (1983) of a relationship between passive smoking and lung cancer in non-smoking women was based simply on the observation that the proportion of female non-smoking lung cancer patients living together with a smoker exceeded the proportion of male smokers as reported in the previous microcensus, ignoring *inter alia* the fact that in many families women live with more than just their husbands.

In the present study no significant relationship of passive smoking to lung cancer incidence in lifelong non-smokers was seen, either in the analyses based on the information collected in hospital or in subsequent inquiry of the spouses or both. It must be pointed out, however, that the number of lung cancer patients who had never smoked was rather small so that, though our findings are consistent with passive smoking having no effect on lung cancer risk at all, they do not exclude the possibility of a small increase in risk, though the upper 95% confidence limit of 1.50 for the estimate of 0.80 (Table IV) in relation to the spouse smoking during the whole of the marriage is not consistent with some of the larger increases claimed by Hirayama (1981, 1984) Trichopoulos *et al.* (1981, 1983) and Correa *et al.* (1983).

Though the number of lung cancer patients who had never smoked is small, varying around 30–50 depending on the analysis, this number is not very different from that reported in a number of other studies, e.g. the findings of Correa *et al.* (1983) were based on only 30, while those of Trichopoulos *et al.* (1981), even when updated (Trichopoulos *et al.*, 1983) were based on only 77. The difficulty of obtaining an adequate sample size is underlined when one considers that in our study the 44 never smoking lung cancer patients who completed passive smoking questionnaires in hospital were extracted from a total of 792 lung cancer patients. It would need a very large research effort to increase precision substantially, and even then one would have to take care that the magnitude of any biases did not exceed the magnitude of the effect one was looking for.

The two major prospective studies which have so far reported findings on passive smoking (Hirayama, 1981; Garfinkel, 1981) were not actually designed to investigate this issue and, as a result, could only use spouse's smoking as an index of exposure. Our study, on the other hand, though not able to monitor exposure objectively, as would have been preferable, was able to look at passive smoking in a wider context, by asking about the extent of exposure at home, at work, during travel and at leisure. Although the answers to these questions were subjective, and could have exhibited some bias, their inclusion perhaps allows greater confidence in the conclusions.

It was interesting that, of the 59 patients for whom spouse's cigarette smoking habits were obtained from both the spouse and the patients, there were 9 (15%) patients for whom there was disagreement as to whether the spouse had been a smoker at some time during the marriage. It seems reasonable to suppose that some of these were in fact smokers and may have been erroneously classified as non-smokers had only one source of information been used. It was also noteworthy that there was quite a strong correlation in our study between active and passive smoking. As illustrated in Table VI, current smokers were considerably more likely to be exposed to passive smoke exposure at home (from sources other than their own cigarettes) than were never or ex-smokers. As noted above, this correlation, coupled with some misclassification of smokers as non-smokers, may spuriously inflate the estimate of risk related to passive smoking. It is important to carry out further studies to obtain more accurate information on reliability of statements about smoking habits because of this possibility of bias.

Little other evidence is available concerning the relationship between passive smoking and risk of the other smoking-associated diseases in (adult) non-smokers and much of this is open to criticism. In his original paper, Hirayama (1981) presented relative risks of death for various diseases for non-smoking women according to the husband's smoking habits. Based on a total of 66 deaths, a slight positive trend for emphysema and asthma was not significant, while, based on a total of 406 deaths, no indication of a trend at all was seen for ischaemic heart disease. In a later paper, based on

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Table VI Relative odds of having passive smoke exposure at home according to patient's own manufactured cigarette smoking habits (standardised for age base = combined class 1 and 2 controls)

Own smoking habits	Relative odds (95% confidence limits)	
	Male	Female
Never	1	1
Ex	1.25(0.86–1.81)	1.26(0.86–1.85)
Current	4.00(2.67–5.98)	2.51(1.74–3.62)
Chi-squared for trend (2 df)	57.81	25.34
P	<0.001	<0.001

only a further 88 ischaemic heart disease deaths. Hirayama (1984) reported a slight positive trend in risk, but this was not statistically significant. Garland *et al.* (1985), in a small prospective study, reported a 15-fold higher risk of ischaemic heart disease in non-smoking Californian women whose husbands were current or former smokers compared with those whose husbands were never smokers, but this enormous and implausible relative risk was only significant at the 90% confidence level and had very wide confidence limits, being based on only 2 deaths in women whose husbands were current smokers. Sandler *et al.* (1985), in a case-control study carried out in North Carolina, reported a strong relationship between risk of cancer of all sites and passive smoking. This study has been criticised by Lee (1985) who notes that it is basically implausible that passive smoking should increase risk of cancers not associated with active smoking. Lee also criticised the method of analysis, showing that no association with cancer risk would be found if a more standard method of analysis was used. Vanderbroucke *et al.* (1984), based on a 25 year follow-up of 1,070 Amsterdam married couples, recently reported that passive smoking was associated with some decrease in total mortality.

There is evidence indicating that young children whose parents smoke have an excess incidence of respiratory symptoms and some reduction in pulmonary function. Reviewing this evidence, Lee (1984) noted that the interpretation of the association is fraught with difficulties and that other possible explanations, including social class related factors, parental neglect, nutrition, cross-infection and smoking during pregnancy, had not been taken into account adequately, so that a causal effect of passive smoking could not be inferred. The relevance of these findings to chronic bronchitis or other diseases in adults is in any case not clear.

Our analyses showed no significant effect of passive smoking on lifelong non-smokers as regards risk of chronic bronchitis, ischaemic heart disease or stroke. In all the analyses relating the various indices of passive smoke exposure to these diseases, no significant differences were seen and slight decreases in risk were as common as slight increases.

While more data would be desirable for these diseases, lung cancer continues to be the major smoking associated disease for which passive smoking comes under suspicion. Since all the difficulties of carrying out good research have clearly still not yet been overcome, further research is certainly needed. Our findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

Any views expressed in this paper are those of the authors and not of any other person or company.

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Brownson, R.C., Reif, J.S., Keefe, T.J., Ferguson, S.W. and Pritzl, J.A., "Risk Factors for Adenocarcinoma of the Lung," American Journal of Epidemiology 125(1): 25-34, 1987.

Microscopically confirmed pulmonary adenocarcinoma cases and controls (group-matched for age and sex) were examined in this Denver, CO case-control study. A total of 102 cases and 131 controls were included; 50 cases and 65 controls were male, 52 cases and 66 controls were female. Cases were located through the Colorado Central Cancer Registry; controls were individuals with cancer at other sites. Proxy interviews were conducted for 68.6% of cases and 38.9% of controls. The study's focus was the evaluation of the roles of smoking, "passive smoking," occupation, air pollution and socioeconomic status in the etiology of adenocarcinoma.

Exposure estimates were spousal smoking status and number of hours per day spent in the presence of a smoker. For the former, RRs of 1.40 (95% CI 0.66-2.14) for males and 1.54 (95% CI 0.72-2.35) for females were reported; for the latter, reported RRs were 1.01 (95% CI 0.42-2.41) for males and 2.42 (95% CI 0.94-6.22) for females. The authors claimed that their data suggested a statistically significant trend for the number of hours/day "passive smoke exposure" in females; the lowest exposure category was 0-3 hours/day.

Potential confounding factors of income and occupation were included in a multiple logistic regression analysis.

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RISK FACTORS FOR ADENOCARCINOMA OF THE LUNG

ROSS C. BROWNSON,[1,3] JOHN S. REIF,[1] THOMAS J. KEEFE,[1] STANLEY W. FERGUSON,[2] AND JANE A. PRITZL[2]

Brownson, R. C. (Dept. of Microbiology and Environmental Health, Colorado State U., Fort Collins, CO 80523), J. S. Reif, T. J. Keefe, S. W. Ferguson, and J. A. Pritzl. Risk factors for adenocarcinoma of the lung. *Am J Epidemiol* 1987;125:25–34.

The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979–1982 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (odds ratio (OR) = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% confidence interval (CI) = 0.39–2.97) for passive smoke exposure of four or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% CI = 0.97–5.12). The results suggest the need to develop cell type-specific etiologic hypotheses.

air pollution; lung neoplasms; tobacco smoke pollution

Recent evidence indicates that lung cancer may encompass several morphologically and clinically distinct diseases (1, 2). In industrialized western nations, incidence rates are highest for squamous cell carcinoma, followed by adenocarcinoma (3, 4). The relation between squamous cell and small cell carcinomas and cigarette smoking is well-established, but the relation between adenocarcinoma and cigarette smoking is less clear (3, 5, 6).

Adenocarcinoma is the most frequently diagnosed form of lung cancer in the United States among women and nonsmokers (3, 7). In a series of nearly 30,000 cases of primary lung cancer, 22 per cent were spec-

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[1] Department of Microbiology and Environmental Health, Colorado State University, Fort Collins, CO.
[2] Colorado Department of Health, Denver, CO.
[3] Reprint requests to Dr. Ross C. Brownson at current address: Cancer Epidemiology and Control Program, Division of Environmental Health and Epidemiology Services, Missouri Department of Health, P. O. Box 1268, Columbia, MO 65205.
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ified as adenocarcinoma among males compared with 37 per cent among females (8). The role of occupational exposures in the etiology of adenocarcinoma remains inconclusive (9, 10). Recently, a disproportionate increase in the incidence of adenocarcinoma has been noted in the United States (5). The changing histologic patterns of lung cancer incidence may be due to a change in diagnostic practices and classification or to increasing exposure to environmental carcinogens.

The present investigation was designed to evaluate the role of smoking, passive smoking, occupation, community air pollution, and socioeconomic status in the etiology of adenocarcinoma of the lung. A case-control study was conducted to provide additional data concerning the relation between exposure variables and this infrequently studied and poorly understood form of lung cancer.

Materials and methods

Cases and controls were identified through the population-based Colorado Central Cancer Registry maintained by the Colorado Department of Health. For the years and counties included, reporting was essentially complete. All diagnoses were microscopically confirmed and classified according to histologic type. Study participants were required to have resided in the Denver metropolitan area for at least six months prior to cancer diagnosis in order to reduce migration bias.

Case selection

A total of 149 eligible cases of adenocarcinoma (*International Classification of Diseases* (ICD) code 163) were identified in the five-county Denver metropolitan area from 1979–1982. Selection was restricted to white males and white females. These adenocarcinoma cases were stratified by age and sex. Of the 149 eligible cases, 31 could not be located, 15 refused to be interviewed, and one did not qualify. A total of 102 case interviews (50 males and 52 females) were completed. The mean ages for male and female cases were 64.9 and 66.3 years, respectively.

Control selection

Controls were chosen from persons in the Colorado Central Cancer Registry who had cancer of sites considered to be unrelated to cigarette smoking. Specifically, persons with cancers of the colon (ICD code 153) and bone marrow (ICD code 169) diagnosed from 1979–1982 were chosen as controls and group-matched to adenocarcinoma cases according to age and sex. Matching was done at the group level so that the maximum number of cases and controls could be used in the analyses. Only whites were included in the study, and at least one control was required for each case within each age and sex stratum.

A total of 169 eligible controls were identified. Of these, 24 could not be located, 13 refused to be interviewed, and one did not qualify. A total of 131 usable interviews (65 males and 66 females) were completed. Among controls, 80 were colon cancer patients, and 51 were diagnosed with leukemia. The mean ages for male and female controls were 65.2 and 68.2 years, respectively.

Data collection and analyses

Epidemiologic data were collected by personal interview. The interviewer was unaware of whether the patient was a case or a control. A higher percentage of the interviews in the case group (68.6 per cent) than in the control group (38.9 per cent) were completed by a relative or a friend. Among the 70 nonsurviving cases, 56 interviews were completed with a spouse, seven interviews with a child, six with a sibling, and one with a close friend. For the 51 deceased controls, information was obtained from 42 spouses, six children, two siblings, and one close friend.

Socioeconomic status was assessed by examining two variables, education and income. Educational level was characterized by the highest grade of formal education completed. Gross income was ascertained

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for the previous year, or in case of retirees, for the year prior to retirement.

Smoking history was characterized for cigarettes, cigars, or pipefuls in terms of pack-years of exposure. Passive smoking data were analyzed as a dichotomous variable based on the smoking status of the patient's spouse and as a stratified variable based on the hours per day that the subject was in the presence of persons who were smoking.

Occupational data were analyzed according to industrial category, occupational category, and a self-assessment of the exposure of the respondent to known lung carcinogens in the workplace. Those industries and occupations known to be associated with an elevated risk for lung cancer were coded and multiplied by the number of years in each category to estimate exposure over time (11–13). In addition, each subject was shown a list of 12 groups of materials known to be lung carcinogens and was asked whether he or she had been exposed to the substances during a particular occupation. Pulmonary carcinogens included materials such as asbestos, chromium, nickel, uranium ore, and mustard gas. Positive responses were coded as integers and summed.

An index of exposure to community air pollution was developed based on estimated levels of total suspended particulates per census tract and the years of residence in each census tract (14). Total suspended particulate air pollution, which contains a benzene soluble fraction, was used as an indicator of polycyclic hydrocarbon (e.g., benzo[*a*]pyrene) levels. The total suspended particulate data were stratified into 10 air pollution exposure subgroups, and each census tract within the Denver area was assigned to a subgroup. The residence code consisted of years at each residence multiplied by the corresponding total suspended particulate exposure subgroup.

In the first set of analyses, stratified contingency tables were constructed to adjust for age and smoking for the primary risk factors (15–17). Odds ratios for each level of exposure were calculated by Miettinen's standardized rate technique which controls for confounding factors (18). All analyses included adjustment for age based on the categories 30–49, 50–59, 60–69, 70–79, and 80–99 years. An extension of the Mantel-Haenszel procedure was used to statistically evaluate overall trends in the proportion of cases according to level of exposure to risk factors (19, 20).

Multiple logistic regression was used to obtain maximum likelihood point and interval estimates of the odds ratio, as well as to control for the effects of various confounding risk factors (21–23). The most significant predictors, based on the Mantel-Haenszel results, were included in the logistic model. The dependent variable in these analyses was lung adenocarcinoma (case (coded as 1) or control (coded as 0)). Independent variables were entered in intervals, as recommended by Schlesselman (24). In order to identify the potential confounding effect of the induction period of cancer, the exposure of each case or control to ambient air pollutants and industrial carcinogens was analyzed in two ways: 1) the entire residence and work history of each person was included, and 2) only exposures that took place 10 or more years prior to the time of diagnosis were considered. The analyses were completed both for all subjects and for primary respondents only, to assess the validity of the surrogate interview data. A multiple logistic regression model was also constructed for nonsmoking female cases and controls.

RESULTS

[redacted] (table 1). The age-adjusted odds ratio for prior cigarette use among males was 4.49 (95 per cent confidence interval (CI) = 1.44–13.98). Among females, the risk due to cigarette smoking was 3.95 (95 per cent CI = 1.76–8.80). For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at

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TABLE 1

Adjusted odds ratios (OR) and trend tests for adenocarcinoma of the lung according to level of cigarette use and passive smoke exposure, metropolitan Denver, CO, 1979–1982

Factor	Males			Females		
	No. of cases	No. of controls	OR*	No. of cases	No. of controls	OR
Prior cigarette use (pack-years)						
0	4	19	1.00	19	47	1.00
1–39	14	19	4.06	10	13	1.68
≥40	32	27	7.68	23	6	14.80
Trend (*p* value)			(<0.01)			(<0.01)
Passive smoke exposure (hours/day)						
0–3	16	28	1.00	29	53	1.00
4–7	19	24	1.76	11	8	3.06
≥8	15	13	2.68	12	5	2.33
Trend (*p* value)			(0.46)			(0.05)

* Odds ratio for prior cigarette use adjusted for age; odds ratio for passive smoke exposure adjusted for age and smoking.

different levels of passive smoke exposure followed an overall trend, statistically significant at the 0.05 level. The age- and smoking-adjusted odds ratio for passive smoke exposure (using 0–3 hours per day as the reference level) was 1.01 (95 per cent CI = 0.42–2.41) among males. The corresponding risk for females was 2.42 (95 per cent CI = 0.94–6.22). Odds ratios for passive smoke exposure were also calculated on a yes/no basis for the regular smoking history of the patient's spouse. The adenocarcinoma risk from smoking by the spouse was not significant for males (odds ratio (OR) = 1.40, 95 per cent CI = 0.66–2.14) or females (OR = 1.54, 95 per cent CI = 0.72–2.35).

The odds ratios and their 95 per cent confidence intervals for education level, income, community air pollution exposure history, and occupational exposures are presented in table 2. The lowest level of each variable was used as the reference category. Both education and income showed inverse trends with adenocarcinoma risk. Among males, annual income approached statistical significance with an odds ratio of 0.47 (95 per cent CI = 0.19–1.19). No significant risks in the age- and smoking-adjusted odds ratios were shown for males or females according to their air pollution exposure history. No difference was noted regardless of whether the entire residence history of the patient or only the residence history 10 or more years prior to cancer diagnosis was used in the analysis. Of the occupational variables (industrial category, occupational category, or self-reported exposure to lung carcinogens), only occupational exposures for males bordered on significance (OR = 2.23, 95 per cent CI = 0.97–5.12).

The multiple logistic regression risk estimates for income, occupation, pack-years of cigarette use, and passive smoke exposure are shown in table 3. For both sexes combined, annual income showed an inverse association with adenocarcinoma risk after adjustment for other risk factors (OR = 0.85, 95 per cent CI = 0.72–0.98). A positive association between pack-years of cigarette use and cancer risk was found for males, females, and both sexes combined. The largest risk for adenocarcinoma associated with passive smoking was shown for females at the exposure level of 4–7 hours per day (OR = 1.91, 95 per cent CI = 0.78–3.03). The first-order interaction of pack-years of smoking and passive smoking was examined and found to be nonsignificant.

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TABLE 2

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for adenocarcinoma of the lung according to education, income, air pollution residence history, and occupation, metropolitan Denver, CO, 1979–1982

Factor	Males			Females		
	n	OR*	95% CI	*n*	OR	95% CI
Education level (highest grade)						
0–8	25	1.00		17	1.00	
9–17	90	0.59	0.23–1.54	101	0.73	0.23–2.31
Annual income (thousands of dollars)†						
<$15,000	25	1.00		37	1.00	
≥$15,000	86	0.47	0.19–1.19	78	0.71	0.28–1.85
Residence history (exposure-years)‡						
0–99	26	1.00		31	1.00	
≥100	89	1.66	0.66–4.19	87	1.51	0.58–3.96
Occupation (exposure-years)§						
0	76	1.00		112	1.00	
≥1	39	2.23	0.97–5.12	6	0.59	0.09–3.51

* Odds ratio adjusted for age and smoking.

† Missing values.

‡ The product of years at each residence and the corresponding total suspended particulate exposure subgroup.

§ Occupations at high risk for lung cancer multiplied by the number of years in each category.

TABLE 3

Multiple logistic regression odds ratios (OR) and 95% confidence intervals (CI) for adenocarcinoma of the lung according to income, occupation, cigarette use, and passive smoke exposure, metropolitan Denver, CO, 1979–1982

Factor	All subjects			Males			Females		
	n	OR*	95% CI	*n*	OR	95% CI	*n*	OR	95% CI
Income	233	0.85	0.72–0.98	115	0.85	0.66–1.03	118	0.84	0.64–1.03
Occupation	233	1.00	0.96–1.04	115	1.00	0.97–1.04	118	0.94	0.51–1.37
Pack-years									
0	89	1.00		23	1.00		66	1.00	
1–39	56	2.62	1.82–3.41	33	3.74	2.37–5.12	23	1.93	0.88–2.99
≥40	88	5.81	5.01–6.61	59	5.42	4.13–6.71	29	9.58	8.31–10.86
Passive smoking (hours/day)									
0–3	126	1.00		44	1.00		82	1.00	
4–7	62	1.24	0.53–1.95	43	0.84	0.00–1.80	19	1.91	0.78–3.03
≥8	45	1.37	0.54–2.20	28	1.17	0.10–2.24	17	1.21	0.00–2.68

* Odds ratio adjusted for age, potential confounding factors, and sex when appropriate.

Logistic regression was conducted by using only primary respondents. These results were similar to those found when all respondents were included. Active smoking was the only risk factor significant at the 0.05 level based on the analysis of primary respondents. The odds ratios for pack-years of smoking were consistently smaller for primary respondents, whereas those for passive smoke exposure were larger when primary respondents were analyzed.

The risk of adenocarcinoma due to passive smoke exposure was examined among female nonsmokers (table 4). Nineteen female nonsmoking cases were identified (36.5 per cent). Due to size limitations, passive smoking was divided into two categories: 0–3 and four or more hours per day. An odds ratio of 1.68 (95 per cent CI = 0.39–2.97) was computed for the larger exposure category after adjustment for age, income, and occupation.

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TABLE 4

Multiple logistic regression odds ratios (OR) and 95% confidence intervals (CI) for adenocarcinoma of the lung according to income, occupation, and passive smoke exposure among female nonsmokers, metropolitan Denver, CO, 1979–1982

Factor	n	OR*	95% CI
Income	66	0.85	0.60–1.11
Occupation	66	0.004	
Passive smoking (hours/day)			
0–3	56	1.00	
≥4	10	1.68	0.39–2.97

* Odds ratio adjusted for age and potential confounding factors.

DISCUSSION

Numerous case-control studies of lung cancer have been conducted over the past 30 years. Few, however, have examined the data according to histologic type. There appears to be a general consensus that the various histologic types of lung cancer have a multifactorial etiology which includes cigarette smoking and occupational and other environmental factors.

Smoking is the major risk factor for most types of lung cancer. In the United States, it is estimated that cigarette smoking may contribute to at least 80–90 per cent of lung cancer in males and 40 per cent in females (25). Several reports have suggested that smoking may not be the major risk factor for adenocarcinoma in certain populations (26–28). Among white males, the age-standardized relative risk estimates for lung adenocarcinoma according to prior cigarette use have ranged from less than one at low levels of smoking to about six at high levels of smoking (3, 29). Risk estimates of adenocarcinoma from smoking for females are commonly lower and vary widely among racial groups; for example, the relative risk estimates range from about one in Chinese women to four in Japanese women, and five in Hawaiian women (26, 30). The risk of smoking and adenocarcinoma for white females is usually between one and three, although the risk of lung cancer by histologic type has been studied less frequently among females than among males (10, 30–32).

The current study found significant risk estimates for adenocarcinoma associated with smoking of 4.49 for males and 3.95 for females. The age-standardized risk estimates at different levels of cigarette use showed significant trends ($p < 0.01$) for males and females, indicating that a dose-response relation between smoking and adenocarcinoma was present. The risk estimates based on multiple logistic regression analyses for smoking were generally lower than the odds ratios calculated by the methods of Mantel and Haenszel (15) and Miettinen (17), since logistic regression allowed for adjustment for multiple factors. The risk estimates for smoking and adenocarcinoma found in this study and the presence of a dose-response relation were consistent with other studies (29, 31, 33).

The effect of involuntary inhalation of sidestream smoke (passive smoking) on lung cancer etiology is a controversial current public health issue (34). Hirayama (35) reported a significant relative risk for lung cancer of 2.08 among wives of heavy smokers. A study conducted among Greek women found relative risks of 2.4 and 3.4 for wives of light and heavy smokers, respectively (36). A case-control study in Louisiana identified an increased risk for lung cancer among nonsmokers married to heavy smokers and for subjects whose mothers smoked (37). Garfinkel et al. (38) found an increased lung cancer risk for women whose husbands smoked 20 or more cigarettes per day. A recent study in Los Angeles found a slight increase in risk of adenocarcinoma among nonsmoking women exposed to passive smoke (39). Several other studies have failed to link passive smoke exposure to an increased risk of lung cancer (40–42). Prior studies that have evaluated passive smoking and lung cancer have differed in the index of passive smoke exposure, cell type, and degree of histologic verification (34).

In the present study, indexes of passive smoke exposure were obtained in two ways:

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1) by ascertaining the regular smoking history of the spouse of each subject on a yes/no basis; and 2) by determining the average hours per day that the subject was exposed to smoking (at home and at work). No significant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. When the data were stratified according to level of passive smoke exposure, a statistically significant trend in the risk estimates was shown for females ($p = 0.05$) after adjustment for age and cigarette smoking. However, after adjustment by logistic regression for age, income, occupation, and cigarette smoking, no significant adenocarcinoma risk for passive smoke exposure was found among females.

The relatively large proportion of nonsmoking female cases (36.5 per cent) observed in this study suggested the importance of other risk factors in adenocarcinoma etiology. A previous study found 19.5 per cent nonsmokers among female adenocarcinoma cases (39). Our study demonstrated a slightly elevated risk among female nonsmokers due to passive smoke exposure, consistent with the findings of Wu et al. (39). Deficiencies in passive smoking data in recent studies include: 1) no commonly established index of sidestream smoke exposure; 2) a lack of data on other indoor air pollutants such as radon; 3) the existence of a probable differential in accuracy of obtaining passive smoke exposure histories between living and deceased subjects; 4) a lack of evidence of changes in the peripheral bronchial epithelium of nonsmokers exposed to sidestream smoke (40); and 5) insufficient numbers of nonsmoking lung cancer cases available for analyses. Despite these limitations, the relation between passive smoking and lung cancer deserves further investigation.

Although pollutants in the air have long been suspected to contribute to the etiology of lung cancer, epidemiologic evaluation has been hampered by difficulties in defining and measuring air pollution and in evaluating the effects of confounding variables such as smoking, occupation, and population mobility (43). A census tract analysis of lung cancer data, total suspended particulate air pollution, and median household income was reported previously for the Denver area (14). Our previous work showed a significant direct relation between male lung cancer rates and total suspended particulate air pollution ($p < 0.02$). However, for both males and females, median household income explained a larger percentage of the variation in lung cancer rates than did particulate air pollution.

The data on residence history of cases and controls were analyzed to determine if differences in total suspended particulate air pollution exposure may have accounted for a portion of the adenocarcinoma incidence. There were only slight differences between cases and controls in mean or median years of residence in metropolitan Denver. Residence history was defined in terms of exposure-years (years of exposure to high or low total suspended particulates) in order to define an index of exposure for each case and control. Although, in Denver, cases commonly experienced more exposure-years, no significant differences between cases and controls were detected for males or females. Our data failed to show the presence of a large air pollution effect.

Occupational exposures may be important risk factors for lung cancer (44–51). Prior studies of lung cancer have demonstrated an increased risk for exposure to substances such as asbestos, arsenic, nickel, radon daughters, diagnostic radiation, and fossil fuel combustion products (44). Inconsistent findings have been reported regarding the importance of occupational factors in adenocarcinoma incidence (9, 10). In this study, occupational risks for adenocarcinoma were examined in two ways: 1) an a priori listing of industries and occupations in which workers are at high risk for lung cancer was used to code the work history data from each case or control; and 2) each subject was asked if he or she was ever exposed to a list of known lung carcinogens

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in the workplace. The exposures (industrial, occupational, or pulmonary carcinogens) were cumulated over the lifetime of the subject, and the analysis was based on a classification of any or no previous exposure. Only high-risk occupational history showed a borderline significant risk for adenocarcinoma among males after adjustment for age and smoking history. The occupational risk was smaller after multiple adjustment for age, income, cigarette smoking, and passive smoking. The relations between workplace exposures and adenocarcinoma risk were unchanged regardless of whether the entire work history of the subject or only the work history 10 or more years prior to diagnosis was used.

A difference in risk for lung cancer by social class has been observed whether measured primarily by occupation, income, or education (3). Part of the socioeconomic differential in lung cancer risk is due to smoking habits (52). In this study, education level and gross income were used as socioeconomic indicators. Income level showed a stronger association with adenocarcinoma risk after controlling for age and smoking than did education. Since colon cancer is correlated with socioeconomic status (53), it is possible that the use of colon cancer patients as controls in this study magnified the observed inverse relation between adenocarcinoma and income level. No statistically significant inverse association was noted in adenocarcinoma risk with respect to education level, although risk estimates were commonly lower at higher educational levels.

The issue of dietary vitamin A and lung cancer risk was not addressed in this study. Evidence is accumulating that a deficiency in dietary vitamin A may result in a higher risk for lung cancer and that a higher intake of vitamin A and its provitamins has an apparent protective effect (28, 54–59). Diet may be less important in our study since recent data have suggested that the inverse relation between vitamin A intake and lung cancer is strong for squamous cell and small cell carcinomas but not for adenocarcinoma (29, 58).

This study used a higher proportion of surrogate interviews for cases (68.6 per cent) than of surrogate interviews for controls (38.9 per cent). Several investigators have attempted to characterize the validity of information obtained from surrogate interviews (60–62). Pickle et al. (60) found that siblings were best able to describe events that occurred early in life, whereas spouses and offspring best recounted events during adult life. Other studies have found that bias may be introduced because of inaccurate work histories given by next of kin (61) and that spouses may provide accurate demographic information and a crude estimate of smoking, but details of employment history and diet may be of lower validity (62). To address this problem, we conducted separate analyses for all respondents and for primary respondents. The results were highly comparable and indicated that some conclusions based on all respondents may have been conservative since adenocarcinoma risk estimates for passive smoking were commonly higher among primary respondents.

In light of the changing histopathologic patterns of lung cancer, the findings of this and other recent studies suggest the need to consider the various lung cancer cell types as different diseases. Future research should emphasize accurate histologic typing and the development of cell type-specific etiologic hypotheses.

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ERRATA

The *Journal* has been notified by Dr. Ross Brownson of some errors that went undetected by his co-authors and himself in the "Materials and Methods" section of their recent article, "Risk Factors for Adenocarcinoma of the Lung" (*Am J Epidemiol* 1987;125:25–34). The authors used the nomenclature of the *International Classification of Diseases for Oncology* (ICD-O). Due to a typing error in the manuscript, the topography code they cite for adenocarcinoma of the lung, 163, is incorrect. The correct ICD-O code, and the one they used in the study, is 162, including morphology codes 81403, 82303, 82503, 82603, and 85503. The code that the authors cite for colon cancer (153) is correct. For cancer of the bone marrow, the code more explicitly is 169.1 (in the article, it is given as 169). The authors hope these oversights have caused no confusion to readers.

The *Journal* regrets an error in the title of table 4 in the recently published article by Khoury et al. entitled "Inbreeding and Prereproductive Mortality in the Old Order Amish. II. Genealogic Epidemiology of Prereproductive Mortality" (*Am J Epidemiol* 1987;125:462–72). In technical editing, the title was incorrectly changed to read "Demographic relative risk (RR) factors..." As correctly worded, the title in full should read: "Demographic risk factors for prereproductive mortality (before age 20 years) (PRM) in the Old Order Amish genealogy by year of birth."

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Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F., "Lung Cancer Among Chinese Women," International Journal of Cancer 40: 604-609, 1987.

The purpose of this case-control study was to explore the roles of a number of risk factors for adenocarcinoma among women in Shanghai; 672 female lung cancer patients and 735 population-based controls were interviewed. Cases were newly-diagnosed women in the urban Shanghai population; controls were randomly chosen within 5-year age strata from the general urban population. Approximately 81% of the cases were histologically verified. Apparently no proxies were used. The authors reported that cigarette smoking was a risk factor in Shanghai women.

ETS exposure was assessed as whether the woman had ever lived with a smoker. For overall exposure during adulthood, the RR was 0.9 (95% CI 0.6-1.4). For husband's smoking, the calculated RRs ranged from 1.1 to 1.7. None was statistically significant, although the value of 1.7, for living more than 40 years with a smoking husband, approached statistical significance (95% CI 1.0-2.9). The authors claimed that there was a trend for increasing lung cancer risk with increasing years of living with a smoking husband. For overall exposure during childhood, the reported RR was 1.1 (95% CI 0.7-1.7).

Among life-long nonsmokers, numerous factors were reported to be associated with statistically significant or non-significant elevations in risk, including history of tuberculosis and other pre-existing lung diseases (RR = 1.2-2.0); hormonal factors (e.g., late menopause (RR = 1.3), decreasing menstrual cycle length (RR = 1.6-2.9)); exposure to cooking oil vapors (e.g., numbers of meals cooked by stir frying or boiling (RR = 1.2-2.6), frequency of smokiness during cooking (RR as high as 2.8), frequency of eye irritation during cooking (RR as high as 2.6)); and use of rapeseed oil (RR = 1.4). No association was found between increased consumption of carotene-rich foods and decreased risk, but overall dietary carotene levels are high in this population.

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LUNG CANCER AMONG CHINESE WOMEN

Yu-Tang GAO[1], William J. BLOT[2], Wei ZHENG[1], Abby G. ERSHOW[2], Cheng Wen HSU[3], Lynn I. LEVIN[2], Rong ZHANG[1] and Joseph F. FRAUMENI, JR.[2]

[1]*Shanghai Cancer Institute, Shanghai, People's Republic of China;* [2]*National Cancer Institute, Bethesda, MD 20892, USA; and* [3]*Shanghai Chest Hospital, Shanghai, People's Republic of China.*

A case-control study involving interviews with 672 female lung cancer patients and 735 population-based controls was conducted to investigate the high rates of lung cancer, notably adenocarcinoma, among women in Shanghai. Cigarette smoking was a strong risk factor, but accounted for only about one-fourth of all newly diagnosed cases of lung cancer. Most patients, particularly with adenocarcinoma, were life-long non-smokers. The risks of lung cancer were higher among women reporting tuberculosis and other pre-existing lung diseases. Hormonal factors were suggested by an increased risk associated with late menopause and by a gradient in the risk of adenocarcinoma with decreasing menstrual cycle length, with a 3-fold excess among women who had shorter cycles. Perhaps most intriguing were associations found between lung cancer and measures of exposure to cooking oil vapors. Risks increased with the numbers of meals cooked by either stir frying, deep frying or boiling; with the frequency of smokiness during cooking; and with the frequency of eye irritation during cooking. Use of rapeseed oil, whose volatiles following high-temperature cooking may be mutagenic, was also reported more often by the cancer patients. The findings thus confirm that factors other than smoking are responsible for the high risk of lung cancer among Chinese women and provide clues for further research, including the assessment of cooking practices.

The age-adjusted annual lung cancer incidence rate among females in Shanghai during the 1970's and 1980's has been about 20 per 100,000 population, one of the highest rates in China and in the world (National Cancer Control Office, 1980; Gao, 1982; Waterhouse *et al.*, 1982; Shanghai Cancer Registry, 1983). Elevated lung cancer death rates have also been observed among Chinese women in other parts of the world, including Hong Kong (Kung *et al.*, 1984; Koo *et al.*, 1985), Singapore (MacLennan *et al.*, 1977) and the United States (Fraumeni and Mason, 1974; Hinds *et al.*, 1981; Green and Brophy, 1982). The high rates of this cancer are surprising since few Chinese women smoke cigarettes (Deng and Gao, 1985). Furthermore, in Shanghai (Zheng and Gao, 1986) and elsewhere, hospital records have indicated that most of the lung tumors are adenocarcinomas, a type of lung cancer less strongly related to smoking (Lubin and Blot, 1984). To explore reasons for the high rates of lung cancer among women in Shanghai, the Shanghai Cancer Institute, in collaboration with the US National Cancer Institute, carried out a population-based case-control investigation. Herein we report the results of this study, quantifying the role of smoking and evaluating a variety of suspected risk factors.

MATERIAL AND METHODS

All newly diagnosed cases of primary lung cancer (9th Revision ICD 162) during the 2-year period February 1984–February 1986 among female residents of urban Shanghai aged 35–69 years were identified by a rapid reporting system for lung cancer established for this study. The system was built upon the existing Shanghai Cancer Registry, the oldest in China (Gao, 1982). Trained staff contacted medical facilities in Shanghai to ascertain new cases, so that interviews could be rapidly scheduled (typically within 2 weeks of diagnosis). The staff reviewed relevant medical records, abstracting data on the basis of diagnosis, histologic type, and the site of the tumor within the lung. Two senior pathologists and 4 senior clinicians were appointed to review the diagnostic information from all cases collected in the study, including X-ray films, cytologic and histologic slides.

Female controls were randomly selected within 5-year age strata from the general population of the Shanghai urban area. The number and age distribution of the controls were determined in advance from the number and age distribution of lung cancer cases reported to the Shanghai Cancer Registry during the period 1980–81. The selection procedure involved randomly choosing a neighborhood committee from among the approximately 1,300 committees in urban Shanghai, then randomly choosing a household group within the committee and ascertaining from existing rosters the names of all females in the appropriate age range. Among these persons, 2 were randomly selected. If the first was absent during the period of study or could not be interviewed, the second was accepted as a control. Tables of random numbers were used in the random sampling.

The cases and controls were interviewed by trained interviewers. A structured questionnaire was used to obtain information on demographic characteristics, exposure to tobacco, dietary and cooking practices, medical conditions, family history of lung cancer, menstrual and reproductive factors, job history and other variables. All completed questionnaires and medical abstracts were checked by a field supervisor, and the information was then abstracted on coding sheets for key-punching and computerization in the United States.

Statistical analyses of the collected data were based on multivariate techniques for case-control data (Breslow and Day, 1980). Logistic regression analyses were used to estimate summary relative risks (RR) of lung cancer associated with various factors, after adjusting for age (<55, 55–59, 60–64, 65–69), smoking (non-smoker; smoked less than 20 years or less than 10 cigarettes/day; smoked 20 or more years and 10–19 cigarettes/day; smoked 20 or more years and 20 or more cigarettes/day), education (no formal education, primary school, secondary school and higher) and other variables, and to evaluate statistical significance. Population attributable risk (PAR) estimates for smoking, adjusted for age, were also derived (Whittemore, 1983).

RESULTS

A total of 765 lung cancer patients were identified during the 2-year period and interviews conducted with 672 (88%). We excluded the 93 patients who died, including 38 ascertained by death certificate only. There were no patients who refused interview. Forty-three percent of the cases were diagnosed by tissue biopsy, 38% by cytology, and 19% by repeated

Address reprint requests from China to Dr. Gao and from other countries to Dr. Blot.

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TABLE I - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH NUMBER OF CIGARETTES SMOKED PER DAY AND DURATION OF SMOKING

Number of cigarettes smoked per day	Duration of smoking							
	< 30 Years				> 30 Years			
	Cases	Controls	RR[1]	95% CI	Cases	Controls	RR	95% CI
< 10	36	45	1.4	0.9–2.2	34	29	2.4	1.4–4.1
10–19	19	11	2.6	1.2–5.7	56	33	3.2	2.0–5.1
20+	13	2	8.9	2.0–40.2	78	10	14.1	7.1–28.0

[1]Adjusted for age and education. Non-smokers are used as the reference group.

TABLE II - RELATIVE RISKS OF LUNG CANCER AMONG NON-SMOKING WOMEN ASSOCIATED WITH YEARS LIVED WITH A SMOKING HUSBAND

Years lived with smoking husband	Cases	Controls	RR[1]	95% CI
< 20	57	99	1.0	—
20–29	63	93	1.1	0.7–1.8
30–39	78	107	1.3	0.8–2.1
≥ 40	48	76	1.7	1.0–2.9

[1]Adjusted for age and education

X-ray films. Among the 542 interviewed cases pathologically or cytologically diagnosed, adenocarcinoma was the predominant cell type accounting for 61% of all cases, 22% were squamous carcinomas, 6% were oat-cell (or small-cell undifferentiated) cancers, and 11% were mixtures and other cell types.

A total of 735 controls were interviewed. Among these 71 (9.7%) were "second" controls, chosen mainly because the first selected control had moved from the Shanghai urban area or was found to be outside the eligible age range. The distributions by age, education and marital status were generally similar between cases and controls. More controls than cases (32% *vs.* 20%), however, were in the oldest age group of 65–69 years, but all subsequent analyses were age-adjusted.

Cigarette smoking

Cigarette smoking was associated with a significantly increased risk of lung cancer, even though only 35% of the lung cancer patients (compared to 18% of the controls) had ever smoked. There was a 3.3-fold excess risk (95% CI = 2.5–4.2) of lung cancer among smokers, but risks were higher for squamous-cell carcinoma (RR = 7.2, 95% CI = 4.6–11.1) and oat-cell cancer (RR = 7.2, 95% CI = 3.6–17.0) than for adenocarcinoma (RR = 1.5, 95% CI = 1.0–2.1). The RR for all lung cancers combined tended to rise with increasing numbers of cigarettes smoked per day and with increasing duration of smoking (Table I). The excess reached 14-fold for females who smoked 20 or more cigarettes per day for more than 30 years. Similar trends existed for adenocarcinoma and for squamous/oat-cell cancers, but the magnitude of the increase was considerably greater for the latter (not shown).

We calculated population-attributable risk (PAR) estimates for smoking in each age group. The PAR rose with age, from 8% to 27% to 28% to 40% at ages <55, 55–59, 60–64, and 65–69, respectively, primarily because the prevalence of smoking rose with age. In total, we estimated that 24% of all female lung cancers in Shanghai were due to smoking.

Passive smoking

No significant increase in risk was observed for overall exposure to environmental tobacco smoke during childhood (RR = 1.1, 95% CI = 0.7–1.7) or adult life (RR = 0.9, 95% CI = 0.6–1.4). For these calculations, exposure was said to occur if the subject had ever lived with a smoker. When exposure was defined in terms of husband's smoking, however, lung cancer risks among non-smoking women tended to increase with the number of years a woman lived with a husband who smoked, the RR reaching 1.7 among those with 40 or more compared to less than 20 years' exposure (Table II). The risk in this heavily exposed group was even higher (RR = 2.9, 95% CI = 1.0–8.9) for squamous- and oat-cell carcinoma.

Previous lung diseases

Since lung cancer in its early stages may be confused with other lung diseases, we excluded non-malignant lung diseases occurring within the 3 years preceding interview in evaluating the effect of prior lung disease upon lung cancer risk. Table III shows that previous tuberculosis, pneumonia and emphysema were significantly associated with lung cancer risk even after adjusting for smoking. Although some individuals reported having 2 or more of these diseases, the excesses for each persisted when those with multiple conditions were excluded. Further analysis (not shown) indicated that the effect of tuberculosis was not related to the use of isoniazid or streptomycin. While tuberculosis and pneumonia were related to both squamous/oat-cell carcinoma and adenocarcinoma of the lung, emphysema and chronic bronchitis were associated only with the squamous- and oat-cell types.

Cooking practices

Soybean and rapeseed oils were the oils used most often for cooking in Shanghai, with over 95% of women reporting the use of both products. Rapeseed oil, however, was reported as the most often used cooking oil by 52% of the cases compared to 45% of the controls. The overall increase in risk associated with rapeseed compared to soybean as the most often used oil was 1.4 (95% CI = 1.1–1.8). Table IV shows that the excess lung cancer risk associated with use of rapeseed oil existed at each level of reported frequency of eye irritation when cooking, a subjective variable representing severity of exposure to cooking vapors. The calculations for this Table excluded the few women who never cooked, and employed as the reference group women who most often used soybean oil but never or rarely reported eye irritation. Table IV also shows that risks of lung cancer were independently related to eye irritation, with the highest risks (RR = 2.8, 95% CI = 1.8–4.3) among those using rapeseed oil and frequently reporting irritation. The patterns were similar for squamous/oat-cell cancer and adenocarcinoma. We also observed, after adjusting for eye irritation, a 60% higher risk for lung cancer among women who reported considerable or somewhat smoky conditions in their homes when cooking, another rough measure of exposure to cooking vapors and to house ventilation (Table V). In addition, the risk ratios increased with the number of different dishes per week prepared by stir frying, deep frying, or boiling (Table VI). In contrast, no significant case/control differences were associated with the type of fuel used for cooking. The RR and 95% CI associated with coal, gas and wood as the usual fuels were 0.9 (0.7–1.3), 1.1 (0.7–1.5), and 1.0 (0.6–1.8) respectively. There was no trend in risk with increasing years of use of coal, the most common cooking fuel in Shang-

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TABLE III - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH PREVIOUS LUNG DISEASES

Past lung diseases	Controls	All cases	RR[1]	95% CI	Squamous/ oat-cell	RR[1]	95% CI	Adeno-carcinoma	RR[1]	95%
None	554	418	1.0	—	80	1.0	—	229	1.0	—
Tuberculosis	61	80	1.7	1.1-2.4	20	2.0	1.1-3.7	42	1.6	1.0-2.5
Pneumonia	35	65	1.9	1.2-3.0	16	1.8	0.9-3.8	26	1.5	0.9-2.7
Emphysema	18	37	2.0	1.0-3.7	19	4.5	2.0-10.3	6	0.7	0.3-2.0
Chronic bronchitis without emphysema	86	112	1.2	0.8-1.7	35	1.4	0.8-2.5	33	0.8	0.5-1.3
Others	30	30	1.3	0.7-2.2	8	1.7	0.7-4.2	13	1.0	0.5-2.0

[1]All risks adjusted for age, education and smoking and relative to women with no reported prior lung disease. Persons with more than one past lung disease are included in each lung disease category.

TABLE IV - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH COOKING OIL USED MOST OFTEN AND FREQUENCY OF EYE IRRITATION WHEN COOKING

Eye irritation when cooking	Oil used most often	Cases	Controls	RR[1]	95% CI
Never or rarely	Soybean	140	214	1.0	—
	Rapeseed	145	193	1.2	0.9-1.7
Sometimes	Soybean	70	72	1.5	1.0-2.3
	Rapeseed	87	63	2.0	1.3-3.0
Frequently	Soybean	59	56	1.4	0.9-2.3
	Rapeseed	90	50	2.8	1.8-4.3
Total	Soybean	269	342	1.0	—
	Rapeseed	322	306	1.4	1.1-1.8

[1]Adjusted for age, education and smoking.

TABLE V - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH FREQUENCY OF EYE IRRITATION AND HOUSE SMOKINESS WHEN COOKING

Eye irritation	House smokiness	Cases	Controls	RR[1]	95% CI
Never/rarely	None/slight	244	380	1.0	—
	Somewhat/ considerable	55	55	1.6	1.0-2.5
Sometimes/ frequently	None/slight	212	200	1.6	1.2-2.1
	Somewhat/ considerable	109	60	2.6	1.8-3.7

[1]Adjusted for age, education and smoking.

TABLE VI - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH NUMBER OF DIFFERENT DISHES PER WEEK PREPARED BY DIFFERENT METHODS OF COOKING

Number of dishes per week	Cases	Controls	RR[1]	95% CI
Stir frying				
⩽20	336	408	1.0	—
20-24	198	211	1.2	0.9-1.5
25-29	48	47	1.2	0.8-1.9
⩾30	34	15	2.6	1.3-5.0
Deep frying				
0	502	594	1.0	—
1	85	68	1.5	1.0-2.1
2	21	15	1.6	0.8-3.2
⩾3	8	4	1.9	0.5-6.8
Boiling				
⩽3	96	124	1.0	—
4-7	390	483	1.0	0.7-1.3
8-11	63	40	1.8	1.1-3.0
⩾12	67	33	2.2	1.3-3.7

[1]Adjusted for age, education and smoking.

TABLE VII - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH DIETARY INTAKE OF VITAMIN A

Vitamin exposure variable	Quartile level of consumption[1]			
	I (High)	II	III	IV
Vitamin A index	1.0	0.6 (0.5-0.9)	0.8 (0.6-1.1)	0.5 (0.4-0.7)
Retinol-rich foods	1.0	0.9 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
Carotene-rich foods	1.0	0.6 (0.5-0.8)	0.5 (0.4-0.7)	0.5 (0.3-0.6)

[1]Risk relative to highest quartile of consumption and adjusted for age, education and smoking. 95% CI in parentheses.

hai. Exposures to coal or other fuel fumes were generally associated only with cooking, since nearly all homes in Shanghai were unheated.

Diet

The women were asked about their usual frequency of consumption during adulthood of 32 commonly eaten foods, including the major contributors of vitamin A. Using Chinese food composition tables to estimate the retinol and carotene content of each food and applying these estimates to its frequency of intake, an index of vitamin A consumption in retinol-equivalent units was constructed. The risks for lung cancer tended to be lower among those with low values of this index (Table VII). This association was accounted for mainly by a lower risk among those with a reduced consumption of carotene-rich foods (the dominant source being dark green vegetables). No effect on risk was found for consumption of the retinol-rich foods (mainly fish, eggs and liver). The patterns were generally similar for squamous/oat-cell cancer and adenocarcinoma, and for smokers and non-smokers.

Menstrual and reproductive factors

The risks of lung cancer were higher among women with shorter menstrual cycle lengths (Table VIII). The association was primarily seen for adenocarcinoma, which showed a strong dose-response relationship. Among women aged 55 years and over with a natural menopause, the risk of adenocarcinoma tended to increase with the total number of menstrual cycles over their lifetime. Some increased risk of adenocarcinoma was seen when natural menopause occurred at age 50 or later (RR = 1.3, 95% CI = 0.9-1.7, after adjusting for menstrual cycle length). No associations were seen with age at menarche, age at first pregnancy, or parity.

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TABLE VIII - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH LENGTH OF MENSTRUAL CYCLE

Length of menstrual cycle (days)	All cases	Controls	RR[1]	95% CI	Squamous oat-cell	RR[1]	95% CI	Adeno-carcinoma	RR[1]	95% CI
>33	43	60	1.0	—	12	1.0	—	18	1.0	—
30–33	272	327	1.6	1.0–2.6	62	0.9	0.4–2.0	124	1.9	1.0–3.5
26–29	241	268	1.6	1.0–2.7	51	0.8	0.4–1.9	127	2.1	1.1–3.9
<26	98	78	2.2	1.3–3.7	23	1.6	0.7–3.9	54	2.9	1.5–5.7

[1]Adjusted for age, education, smoking and regularity of menstruation.

TABLE IX - RELATIVE RISKS OF LUNG CANCER FOR WOMEN EVER EMPLOYED IN MAJOR OCCUPATIONAL GROUPS

	Occupation category[1]	Cases	Controls	RR[2]	95% CI
I–II	Professionals and technicians; leaders of state organizations, party and mass organizations and enterprise units	113	116	1.0	0.7–1.4
III–IV	Office and related personnel; sales workers	75	96	0.7	0.5–1.0
V	Service workers	159	160	1.0	0.8–1.4
VI	Agricultural, forestry, animal husbandry and fishery workers	24	21	1.1	0.6–2.1
VII–IX	Production, transportation and other related workers	436	471	1.1	0.9–1.4
0	Never worked	61	75	1.1	0.7–1.6

[1]Women employed in more than one occupational category are included in each category in which they worked. The coding scheme was based on the system used in the 1982 Population Census of the People's Republic of China (Population Census Office, 1985). [2]Adjusted for age, education and smoking.

Occupation

Most women reported working outside the home, but case/control differences according to major occupational categories were small (Table IX). No major occupations were associated with increased risk of lung cancer. A decreased risk, however, was observed for women ever employed in the cotton textile industry, the largest employer of women in Shanghai. There was a slight increase in the relative risk of lung cancer among women ever employed as cooks (RR = 1.2, 95% CI = 0.6–2.1), but few worked longer than 20 years.

Family history

The cancer patients reported about the same frequency of lung cancer in their mothers (1.0%) and fathers (1.7%) as the controls (1.0% and 1.5%, respectively). The RR, adjusted for age, education and smoking, associated with having a parent with lung cancer was 1.1 (95% CI = 0.6–2.3). More sibs were reported to have lung cancer, but the numbers affected were small (6 cases, 3 controls; RR = 3.0, 95% CI = 0.7–12.5). Only one child, of a control, had lung cancer.

DISCUSSION

The high incidence of lung cancer among women in Shanghai, together with the low prevalence of smoking in the general population, led us to consider a number of possible etiologic factors. While cigarette smoking was an important cause of lung cancer, showing a clear dose-response trend, the majority of lung tumors, particularly adenocarcinomas, occurred among non-smokers.

Environmental tobacco smoke may account for some, but probably few, of the cancers among non-smokers, since there was little or no association with ever having lived with a smoker. Among non-smoking women married to smokers, however, there was an upward trend in risk associated with increasing years of exposure. This latter finding is consistent with reports in other parts of the world. When data from nearly a dozen studies evaluating passive smoking were combined (Blot and Fraumeni, 1986), an overall 30% excess of lung cancer (RR = 1.3, 95% CI = 1.1–1.5) was found among non-smoking women married to smokers, with the RR reaching 1.7 among those most heavily exposed.

Although the causal significance of the relation of prior lung disease to lung cancer remains to be clarified, the high prevalence of previous pulmonary infections may have contributed in part to the high incidence of lung cancer among Shanghai women. Earlier in this century, non-malignant lung disease was one of the leading causes of death in China (Kan, 1981). With the advent of antibiotics and improved living conditions, the incidence and mortality of chronic lung diseases, particularly tuberculosis, declined. Nevertheless, a substantial portion (38%) of the women with lung cancer in this study reported prior lung disease, including 12% who were long-term survivors of tuberculosis, whereas significantly lower percentages of controls reported these diseases. To some extent it is possible that recall or ascertainment bias may contribute to the associations observed with prior lung diseases. The elevated risk of lung cancer following tuberculosis, however, is consistent with recent studies in other countries, and is not explained by cigarette smoking or treatment with isoniazid, a pulmonary carcinogen in laboratory animals (Howe *et al.*, 1979; Hinds *et al.*, 1982; Bakris *et al.*, 1983).

Emphysema was also significantly related to lung cancer, after adjustment for smoking habits, with the excess limited to squamous- and oat-cell carcinomas. This finding adds to the evidence that chronic obstructive pulmonary disease enhances the risk of lung cancer (Skillrud *et al.*, 1986), even when controlling for smoking practices. Also noteworthy is the elevated risk associated with prior pneumonia, especially since an association with lung adenocarcinoma has previously been reported among women in Los Angeles (Wu *et al.*, 1985). While pneumonia typically occurred during adulthood in our study, the finding in Los Angeles primarily concerned childhood infection.

Little evidence was found to implicate the type of fuels used for cooking in lung cancer risk, consistent with findings from

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Hong Kong (Koo *et al.*, 1983). The risks of lung cancer among Shanghai women increased, however, with various measures of exposure to cooking oil vapors. These included the number of different dishes prepared per week by either stir frying, deep frying, or boiling; the frequency of eye irritation when cooking; and the smokiness of the house when cooking. In Chinese wok cooking, regardless of the method used, oil is usually poured into a wok and heated to high temperatures before meat or vegetables are added. Even boiling may entail some exposure to cooking oil vapors, since oil is often added to the water before heating. Consequently, the living quarters may become smoky during cooking, with opportunity for exposure to inhalable cooking oil vapors.

The plausibility of the hypothesis that lung cancer may be related to cooking oil vapors, particularly from rapeseed oils used in Shanghai, is enhanced by recent experimental investigations. In one study the mutagenicity of products from cooking oil was assayed by the Ames test (Qu *et al.*, 1986). The extracts of condensed volatiles of rapeseed oil, refined rapeseed oil, and soybean oil heated at about 270°C were all positive in tester strain TA98 activated with S9. The mutagenicity of the extract from rapeseed oil volatiles was stronger than that from soybean oil volatiles. There was no evidence of mutagenicity in the oils themselves, either heated or unheated. In another study, the extracts of condensed volatiles of rapeseed oil enhanced the yield of micronuclei in polychromatic erythrocytes of the bone marrow of mice, with a clear dose-response relationship, reflecting damage of chromosomes and cell genotoxicity by rapeseed oil volatiles (Chen, 1987). Although these tests often correlate with carcinogenic potential, no bioassay studies have yet been carried out, to our knowledge. If the effect of rapeseed oil smoke on lung cancer incidence is real, the problem is of great importance to populations of eastern central China and other areas of the world where the oil is often used for cooking. Chinese rapeseed oil, which is pressed from seeds of *Brassica campestris*, contains about 50% erucic acid (Chinese Academy of Medical Sciences, 1981), in contrast to rapeseed oil with < 2% erucic acid (Canbra oil), which was recently approved for sale in the United States (Federal Register, 1985).

Several studies have shown that the risk of lung cancer is elevated by a low intake of foods containing vitamin A, particularly as its precursor beta-carotene (Colditz *et al.*, 1987). Although reported mainly in Western countries, this association has also been noted among Chinese women in Singapore (MacLennan *et al.*, 1977). However, we found no evidence of a protective effect among women in Shanghai, where intake of fresh, carotene-rich, dark green vegetables is high by world standards. In fact, a positive association was observed between carotene intake and lung cancer risk in females (in contrast to no association in males). We have no ready explanation for this unusual finding in females, which was observed also in a case-control study of lung cancer in Hawaii (Hinds *et al.*, 1984). However, the protective effect of carotene-rich foods was mainly confined to current smokers in one large-scale study (Ziegler *et al.*, 1986), and thus the effect may be less evident in Shanghai where few women smoke.

A clue to hormonal factors was suggested by an association between menstrual cycle length and lung adenocarcinoma. A 3-fold difference in adenocarcinoma risk was found among Shanghai women reporting short (< 26 days) compared to long (> 33 days) menstrual cycles, with only a weak trend for squamous- and oat-cell cancers. A relation of short menstrual cycles to breast cancer risk has been suggested in data from Sweden (Olsson *et al.*, 1983) and, to a lesser extent, the United States (Sherman *et al.*, 1982). Some increases in lung adenocarcinoma risk were also associated with late menopause and with a high estimated total number of menstrual cycles among women aged 55 and over having a natural menopause. A role of hormonal factors is also suggested by the observation that among non-smokers adenocarcinoma affects proportionately more females than males (Lubin and Blot, 1984), and by the findings of estrogen and progesterone receptors in some lung adenocarcinomas of women (Chaudhuri *et al.*, 1982). We discovered no relation to oral contraceptives or replacement estrogen therapy, but use of these compounds among women in the study group was rare in Shanghai. It seems unlikely that the menstrual patterns of Chinese women contribute greatly to their high lung cancer risk, but the internal consistency of the trends suggests that future studies of lung cancer in China and elsewhere should examine endocrine hypotheses in more detail.

This large population-based case-control study of lung cancer in urban Shanghai has confirmed that cigarette smoking is a strong risk factor among Chinese women, but only accounts for about one-fourth of all newly diagnosed cases. Causes of the remainder are unclear, but occupational factors did not appear to be important, nor did familial tendency to lung cancer. Our data suggest, however, that prior lung diseases, hormonal factors, and cooking practices may be involved. Most provocative are the associations with cooking oil volatiles, and further investigations are needed to evaluate their contribution to the high lung cancer rates among Chinese women in various parts of the world.

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Humble, C.G., Samet, J.M. and Pathak, D.R., "Marriage to a Smoker and Lung Cancer Risk," American Journal of Public Health 77(5): 598-602, 1987.

In this case-control study, 609 lung cancer cases (including 28 lifelong nonsmokers) were matched with 781 controls. Cases were identified using the New Mexico Tumor Registry; controls were chosen via random sampling methods, and were frequency-matched on sex, ethnicity and age (10-yr group). Of the 28 nonsmoking cases, histopathological review was conducted for only 17, and nine of those 17 differed from the Tumor Registry's conclusion. Surrogate respondents were used for 52.4% of the cases overall, and 19 of the 28 neversmokers. Regarding ETS, questions were asked about spousal smoking only. Additional questions were asked about spouse's employment and on-the-job exposures to arsenic, asbestos, lead, pesticides, and radiation.

The authors report a three-fold increase in lung cancer risk for all nonsmokers (males and females combined) whose spouses smoked cigarettes, regardless of adjustments for ethnicity (OR = 3.2, 90% CI 1.5-7.2) or age (OR = 3.2, 90% CI 1.5-7.3). The sample was too small to allow simultaneous adjustment for ethnicity and age. For females only, the OR for spousal smoking of cigarettes only was 1.8 (90% CI 0.6-5.4). The authors claimed that their data supported increasing risk with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse.

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Marriage to a Smoker and Lung Cancer Risk

CHARLES G. HUMBLE, MS, JONATHAN M. SAMET, MD, MS, AND DOROTHY R. PATHAK, PHD, MS

Abstract: As part of a population-based case-control study of lung cancer in New Mexico, we have collected data on spouses' tobacco smoking habits and on-the-job exposure to asbestos. The present analyses include 609 cases and 781 controls with known passive and personal smoking status, of whom 28 were lifelong nonsmokers with lung cancer. While no effect of spouse cigarette smoking was found among current or former smokers, never smokers married to smokers had about a two-fold increased risk of lung cancer. Lung cancer risk in never smokers also increased with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse. Our findings are consistent with previous reports of elevated risk for lung cancer among never smokers living with a spouse who smokes cigarettes. (*Am J Public Health* 1987; 77:598–602.)

Introduction

The causal association of active cigarette smoking with lung cancer has been accepted for many years.[1,2] Recent epidemiologic evidence indicates that involuntary exposure of nonsmokers to tobacco smoke is also associated with lung cancer.[3–5] Nonsmokers, as well as active cigarette smokers, inhale environmental tobacco smoke, which consists of a combination of sidestream smoke and exhaled mainstream smoke. The putative association of environmental tobacco smoke with lung cancer derives biological plausibility from the lack of a demonstrated threshold for lung cancer in active smokers, from the qualitative similarities of mainstream and sidestream smoke, and from the presence of mutagens in the urine of passive smokers.[5,6]

The association of involuntary exposure to tobacco smoke with lung cancer has now been examined in studies conducted in Japan, Greece, Hong Kong, Scotland, Germany, and the United States.[5] These studies generally indicate an increased risk in nonsmokers. Studies from Japan, Greece, and the United States have shown elevated risk estimates associated with the exposure of nonsmokers to their spouses' smoking.[3,4,7–10] Increased risks have not been found in all investigations, although estimates of effect from those reports with negative findings are generally consistent with those from reports showing elevated risks.[11–16]

In 1980 we began collecting data in a population-based case-control study designed to explain differing lung cancer occurrence in Hispanic and non-Hispanic Whites in New Mexico.[17] The original study questionnaire included questions on tobacco smoke exposure from spouse smoking and on indirect exposure to asbestos through a spouse's job. This report describes the risks associated with these exposures in smokers and nonsmokers in New Mexico.

Methods

Case Selection

The cases were Hispanic and non-Hispanic residents of New Mexico, less than 85 years of age at diagnosis of primary lung cancer. Cases were ascertained by the New Mexico Tumor Registry, a member of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.[18] An initial case series was selected from patients with cancer incident between January 1, 1980 and December 31, 1982. For this initial series all cases less than 50 years of age and all Hispanics were included; non-Hispanics age 50 or older were sampled randomly to select 40 per cent of the males and 50 per cent of the females. To increase the size of the female non-Hispanic subgroup and Hispanics of both sexes, we selected additional cases: all patients in these groups with cancer incident between December 1, 1983 and November 30, 1984. Of the 724 eligible cases selected for the study, interviews were completed with 641, or 88.5 per cent. Of the interviews with cases, 305 were completed with the cases themselves and 336 were with surrogates, generally either the surviving spouse or a child.

For the cases in nonsmokers, the histopathological type of lung cancer was classified by panel review of histopathological material (N = 17) or by information in the New Mexico Tumor Registry case abstract (N = 28). The panel, which included two pathologists, determined the histopathological type on the basis of conventional light microscopy and used a modification of the World Health Organization classification.[19,20]

Control Selection

Potential controls were ascertained by two methods. Residences, identified from lists of randomly generated telephone numbers, were called and a household census was taken from the person who answered. Telephone sampling identified 2,038 potentially eligible households, of which 287 (14.2 per cent) refused to cooperate with the census. As this technique was not efficient for selecting older controls, an additional 252 persons were chosen from a list of randomly selected New Mexico residents, 65 years and older, who were on the Health Care Financing Administration's roster of Medicare participants. The control group was frequency-matched to the cases for sex, ethnicity, and 10-year age category at a ratio of approximately 1.2 controls per case. Of the 944 controls selected for this study, 784 (83.1 per cent) were interviewed.

Interview Data Collection

The interviews were conducted by bilingual interviewers. Respondents were asked to describe the smoking habits of all spouses of the index subject. For each smoking spouse, duration of use and average amount smoked daily were recorded for cigarettes, cigars, and pipes. Respondents were not asked to describe exposures to tobacco smoke at work or in other situations outside of the home. All jobs held by a spouse for one year or more also were recorded, as were reports of spouses' on-the-job exposures to arsenic, asbestos, lead, pesticides, and radiation. We hypothesized a priori that asbestos exposure might increase lung cancer risk and

From the New Mexico Tumor Registry, the Departments of Medicine and of Family Community and Emergency Medicine, and the Interdepartmental Program in Epidemiology, University of New Mexico Medical Center, Albuquerque. Address reprint requests to Jonathan M. Samet, MD, New Mexico Tumor Registry, University of New Mexico Medical Center, 900 Camino de Salud NE, Albuquerque, NM 87131. This paper, submitted to the Journal July 18, 1986, was revised and accepted for publication November 17, 1986.

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added the other agents to reduce the emphasis on asbestos and to test for information bias. A detailed history of personal cigarette use was collected from subjects who had smoked for six months or more.

Calculation of Passive Exposure Indices

Measures of passive exposure to tobacco smoke and to asbestos were created by summarizing the information provided for each spouse. For tobacco smoke, categorical and continuous measures of exposure were calculated. We designated as "exposed" subjects ever married to a spouse who smoked cigarettes, regardless of the spouse's use of pipes or cigars. To examine the effects of cigarette smoke alone, subjects whose spouses had smoked other tobacco products were excluded from some analyses. We created two indicator variables for these exposures: one for all forms of tobacco smoke, and the other for cigarette smoke alone. We also calculated the duration of exposure to a cigarette-smoking spouse and the average number of cigarettes smoked daily by the spouse(s). If complete data were unavailable for all marriage partners, these variables were set to unknown.

Two categorical variables were created to describe potential indirect exposure to asbestos through a spouse's job. Spouse's job histories were reviewed against a list of jobs judged a priori as possibly involving exposure to asbestos: asbestos mining, textile manufacturing, auto brake repair, cement or construction work, pipe fitting or covering, insulation work, and shipyard work. If one or more jobs held by the spouse appeared on the list, the index subject was classified as exposed. Similarly, if a spouse was described as exposed at work to asbestos the index subject was considered to be exposed.

Data Analysis

For these analyses, cigarette smokers were those individuals who had smoked at least six months. Current smokers were those still smoking at interview or who had stopped within the previous 18 months; ex-smokers had ceased smoking at least 18 months before interview. The status of cases classified by questionnaire as never smokers was verified against hospital chart summaries on file at the New Mexico Tumor Registry. Of the 28 reported nonsmokers, the summaries showed that three cases had smoked cigarettes and that one case had smoked pipes and cigars regularly. Analyses of the data for never smokers were performed with and without these four subjects. Because the study included only eight males who had never smoked cigarettes, all analyses were performed for females alone and for all subjects combined.

We used the Mantel-Haenszel technique to control for ethnicity and age in estimating odds ratios for passive exposure to cigarette smoke, within strata of personal cigarette smoking.[21] In these analyses, age was categorized as below 65 years or 65 years and greater. Among never smokers, the exposure-response relation of lung cancer risk with average cigarettes smoked daily by the spouse and with duration of passive cigarette exposure was tested using Mantel extension methods for stratified data.[22] For these variables, strata of exposure were defined by the median level among all exposed never smokers. Those never exposed were the reference group for all analyses.

To examine further the effects of the passive exposures, logistic regression models were fitted for smokers and never smokers. All models included adjustment for ethnicity and four categories of age, variables for which the controls had been frequency matched to the cases. In the model for smokers, potential confounding by personal cigarette use was controlled by entering the average daily cigarette consumption, the duration of smoking, years since stopping for ex-smokers, and an interaction term calculated as the product of smoking duration and an indicator variable for age less than 65 years or 65 years and older. This model was selected on the basis of analyses described in more detail elsewhere.[23] The all-subjects models included control for sex. The two categorical indicators of passive exposure were tested individually in each model. Trends in risk with number of cigarettes of exposure daily and with duration were examined by fitting models with indicator variables to define categories of unexposed, exposed at or below the median, and above the median.

TABLE 1—Sex, Ethnicity, and Age Distribution of Subjects by Personal Cigarette Smoking Status in a Case-Control Study in New Mexico, 1980–84

Subjects	Age (years)	Cigarette Smoking Status: Current Case	Current Control	Former Case	Former Control	Never Case	Never Control
Male							
Hispanic							
White	<65	34	22	10	18	0	10
	≥65	47	30	27	29	1	21
Non-Hispanic							
White	<65	77	57	19	59	1	36
	≥65	82	60	62	103	6	63
Female							
Hispanic							
White	<65	11	8	3	7	2	27
	≥65	27	6	5	5	7	34
Non-Hispanic							
White	<65	74	34	8	17	3	47
	≥65	64	15	31	19	8	54

Risk estimation for the effect of indirect exposure to asbestos was limited to females as no males were indirectly exposed. Logistic regression models were employed that controlled for active smoking as described above, for current and ex-smokers, and for marriage to a smoker for never smokers.

Because surrogate interviews were necessary for 52 per cent of the cases, we assessed the effect of information source by performing the analyses separately for self-reported and surrogate-reported cases, using self-reported controls. We excluded from these analyses the 13 controls for whom surrogate interviews had been necessary.

All cross tabulations and logistic models were performed with standard programs of the Statistical Analysis System.[24] Odds ratios (OR) and 90 per cent two-sided Cornfield confidence intervals (CI) were calculated using program 23 from the Rothman and Boice text for programmable calculators.[25,26]

Results

The analyses were restricted to those 1,390 subjects with known passive and personal smoking status (Table 1). The 35 excluded subjects were older than those included (mean age 68.4 vs 65.6 years, respectively). More cases were excluded than controls (5.0 per cent vs 0.4 per cent, respectively), due in part to the greater proportion of surrogate interviews for cases than for controls. The percentage of subjects excluded did not differ by ethnicity or sex.

Based on data in the New Mexico Tumor Registry files, the cases described by interview data as "never smokers"

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TABLE 2—Odds Ratio[a] Estimates for Passive Cigarette Exposure in a Case-Control Study of Lung Cancer in New Mexico, 1980–84

Passive Exposure	Personal Smoking Status	All Subjects OR	All Subjects 90% CI[b]	Females Only OR	Females Only 90% CI[b]
Cigarettes only	Current	1.2	0.9, 1.6	0.9	0.4, 2.2
	Former	1.1	0.8, 1.5	0.7	0.2, 2.2
	Never	2.9	1.3, 6.7	1.8	0.6, 5.4
Cigarettes and/or pipe or cigar	Current	1.2	0.9, 1.6	0.9	0.5, 1.8
	Former	1.1	0.8, 1.5	0.8	0.2, 1.7
	Never	3.2	1.5, 7.2	2.3	0.9, 6.6

[a]From crude cross tabulations; adjustment for age or for ethnicity did not alter results.
[b]Two-sided 90 per cent Cornfield confidence intervals.

TABLE 3—Odds Ratio Estimates from Multiple Logistic[a] Analyses of Passive Cigarette Exposure and Lung Cancer Risk, in a Case-Control Study in New Mexico, 1980–84

Passive Exposure	Personal Smoking Status	All Subjects OR	All Subjects 90% CI	Female Only OR	Female Only 90% CI
Cigarette only	Ever[b]	1.0	0.8, 1.4	1.0	0.5, 1.9
	Never	2.2	1.0, 4.9	1.7	0.6, 4.3
Cigarettes and/or pipe or cigar	Ever[b]	1.0	0.8, 1.3	0.9	0.5, 1.5
	Never	2.6	1.2, 5.6	2.2	0.9, 5.5

[a]All models included variables to control for the frequency matching on age and ethnicity, and sex, when appropriate.
[b]Models for smokers controlled for personal cigarette use as described under Methods.

TABLE 4—Odds Ratio[a] Estimates by Duration of Spouse Cigarette Smoking and by Average Cigarettes Smoked Daily by the Spouse(s) among Never Smokers in a Case-Control Study in New Mexico, 1980–84

Subject Group	Duration ≤26 Years OR	≤26 Years 90% CI	>26 Years OR	>26 Years 90% CI	Chi for trend
All Subjects	2.2	0.8, 5.9	2.7	1.0, 7.1	2.01
Females only	1.6	0.5, 5.8	2.1	0.7, 6.9	1.23
	Mean Cigarettes per Day ≤20 OR	≤20 90% CI	>20 OR	>20 90% CI	
All Subjects	2.8	1.2, 6.6	2.2	0.6, 7.3	1.82
Females only	1.8	0.6, 5.6	1.2	0.3, 5.2	0.46

[a]Odds ratios not adjusted for age or ethnicity. Adjustment for either of these factors did not change the results. The referent category was the never exposed.

who were ever married to a smoking spouse included eight adenocarcinomas, two epidermoid carcinomas, two small cell carcinomas, and four large cell carcinomas. The eight nonexposed cases reported to be never smokers comprised six adenocarcinomas and two epidermoid carcinomas. A specific histological type had not been assigned to four of the cases. Of the four cases in reported never smokers but who were identified by Tumor Registry information as smokers, one was small cell carcinoma, two were adenocarcinoma, and one was not classified. Because material was only retrieved for 17 cases for panel review, we did not compare the exposed and nonexposed based on the pathologists' classification. Of the 17 cases, the cell type based on the panel's review concurred with that in the Registry for only eight cases.

In the never smoking controls, marriage to a smoker of any type of tobacco was reported for 28 per cent of males and for 56 per cent of females. The corresponding percentages for marriage to a smoker of cigarettes alone were similar, 28 per cent for males and 57 per cent for females.

Using stratified and unstratified approaches, no effect of marriage to a smoker was found among current or former cigarette smokers (Table 2). By contrast, among never smokers, cigarette smoking by a spouse, regardless of pipe or cigar use, was associated with a three-fold increased risk of lung cancer. Adjustment for ethnicity (OR = 3.2, 90 per cent CI [Confidence Interval] = 1.5, 7.2) or for age (OR = 3.2, 90 per cent CI = 1.5, 7.3) did not change the estimated risks. A similar close agreement of crude (Table 2) and adjusted estimates was observed for exposure to cigarettes only: ethnicity-adjusted OR = 3.0 (CI = 1.3, 6.8) and age-adjusted OR = 2.9 (CI = 1.3, 6.7). There were insufficient subjects to adjust simultaneously for ethnicity and age. Although the odds ratios were reduced, restriction of the sample to females did not change the pattern of effect from that found in the analyses with all subjects. When the analyses were performed separately for self- and surrogate-reported cases, the odds ratios were comparably elevated for both groups (data not shown). Because the control series did not include sufficient numbers of controls with surrogate interviews, the controls could not be similarly stratified by type of interview.

Odds ratios from the logistic models (Table 3) tended to be lower than from the unstratified and stratified analyses (Table 2). Risk estimates for the current and former smokers from the logistic models also showed no effect of passive cigarette exposure beyond that of active smoking. However, among the never smokers all point estimates were above unity.

Assessment of exposure-response relation for the duration of exposure and for the average cigarettes smoked daily by the spouse was limited to never smokers. For the all-subjects and females-only cross tabular analyses, a pattern of increased risk with greater duration of cigarette exposure was found (Table 4). In contrast, the logistic models did not show an increase with duration of exposure in either group: (for all subjects, short duration OR = 1.9, CI = 0.7, 4.7; long duration OR = 1.8, CI = 0.7, 4.5). The exposure-response pattern for cigarettes smoked daily showed higher odds ratios for subjects whose spouses smoked a pack or less per day than for those whose spouses smoked greater amounts (Table 4). Control of stratification factors by multiple logistic modeling did not change the pattern of higher relative risk estimates for nonsmokers exposed to 20 or fewer cigarettes per day (OR = 2.0, CI = 0.9, 4.6) compared with those exposed at higher levels (OR = 1.6, CI = 0.5, 4.9). The respective logistic estimates for females were lower: OR for daily exposure of 20 cigarettes or less was 1.6 (CI = 0.6, 4.3) while for exposure to more than 20 cigarettes the OR was 1.2 (CI = 0.3, 4.4).

Potential indirect exposure to asbestos was only reported for females. In the controls, 14.5 per cent of women were designated as exposed based on their husband's work history and 8.2 per cent were considered as exposed based on a report of their husband's occupational exposure to asbestos. The effects of the asbestos exposure variables were assessed

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TABLE 5—Estimates of Lung Cancer Risk from Spouse's Occupational Exposure to Asbestos, by Reporting Source, for Females in a Case-Control Study in New Mexico, 1980–84

Personal Smoking Status		Employment in Asbestos-Related Job		
		All Subjects	Self-reported	Surrogate[b] reported
Ever[a]	OR	0.8	0.7	1.1
	90% CI	0.4, 1.6	0.3, 1.5	0.5, 2.8
Never	OR	2.5	1.2	3.3
	90% CI	1.0, 6.4	0.2, 8.2	1.1, 9.5
		Reported as Exposed at Work		
		All Subjects	Self-reported	Surrogate[b] reported
Ever[a]	OR	1.4	1.3	2.0
	90% CI	0.6, 3.2	0.5, 3.4	0.7, 5.5
Never	OR	2.2	2.8	2.0
	90% CI	0.5, 9.2	0.4, 20.7	0.3, 13.9

[a]Both current and former smokers included.
[b]Self-reported controls were the comparison group for the surrogate-reported cases.

with multiple logistic models and found to vary with cigarette smoking habits (Table 5). The odds ratios were higher for the never smoking females; and in these never smokers the two exposure variables gave comparable risk estimates.

Discussion

In the context of a population-based case-control study in New Mexico, we have examined the risk of lung cancer associated with marriage to a cigarette smoker. The results indicated increased risk from this exposure in never smokers, but not in active smokers.

Methodologic limitations of the case-control approach for studying the relation between involuntary exposure to tobacco smoke and lung cancer must be considered. Misclassification of both active and passive exposure to cigarette smoke is of particular concern. With regard to active smoking, we assigned exposure on the basis of a comprehensive interview with either the index case or a surrogate respondent. For four of the 28 cases among never smokers, information in the hospital record conflicted with the interview. Because a similar, additional source of data was not available for controls, we did not exclude the four cases from this report. The findings were unchanged, however, when they were removed from the analyses.

We assessed passive exposure to tobacco smoke only from marriage to a smoking spouse; exposures from other smokers at home and in the workplace were not assessed. Thus, subjects may have been misclassified on total passive smoke exposure. Wald and Ritchie[27] have shown that nonsmoking men married to smoking women report greater exposure to the smoke of others outside of the home than nonsmoking men married to nonsmoking women. Wald and Richie suggest that information on smoking by the spouse conveys some information on other sources of exposure.

Surrogate interviews were necessary for 19 of the 28 never smokers. While the validity of surrogate information has been questioned for some exposures,[28] the surrogate respondents were primarily surviving spouses, who provided information on their own smoking habits and those of previous spouses, if any. Extensive misclassification introduced by the surrogate interviews thus appears unlikely, although spouses aware of the putative association of passive smoking with lung cancer may have minimized their own smoking. Spouse surrogates may have supplied more accurate information concerning their own smoking than would have been available from the index subject. The much higher proportion of surrogate interviews for cases than for controls could have introduced differential misclassification and biased effect measures upwards.

The results of the present case-control study complement those from other case-control studies[4,7–10] and from cohort studies,[3,11] which showed increased lung cancer risks in never smokers married to smokers. The magnitude of the effect of marriage to a smoker in the present study, about a two-fold increase in risk (Tables 2 and 3), is comparable to findings by Hirayama[3] and by Akiba, *et al*,[9] in Japan, by Trichopoulos, *et al*,[4] in Greece, and by Correa, *et al*,[7] and by Dalager, *et al*,[10] in the United States. A weak exposure-response relation was present with duration of passive exposure, but not with average number of cigarettes smoked daily by the spouse (Table 4). In contrast, in a larger case-control study, Garfinkle, *et al*,[8] found a trend of increasing risk for nonsmoking women with the number of cigarettes smoked daily at home by their husbands.

In active smokers, we found that residence with a smoker did not elevate lung cancer risk (Table 2). The lack of association in active smokers is consistent with the quantitative differences in the exposures of active and passive smoking.[6] Furthermore, active smokers must receive more passive exposure to tobacco smoke from their own smoking, than from the smoking of others. The odds ratios for passive smoking in active smokers, all at or near unity, provide evidence against consistent under- or overreporting of exposure (Tables 2 and 3).

We also assessed the effects of marriage to a spouse employed in jobs possibly involving contact with asbestos. We hypothesized that asbestos brought into the home by the spouse might increase lung cancer risk in smokers and nonsmokers. Domestic exposure has been previously associated with mesothelioma, pleural abnormalities, and changes in the lung parenchyma.[29] We used both a lifetime occupational history for the spouse of the index case and reported contact with asbestos to assess possible indirect exposure of the cases to asbestos.

With both approaches for determining exposure, we found associated elevations of risk for lung cancer (Table 5). The effect was more evident in never smokers, although comparable relative risks would be anticipated if cigarette smoking and asbestos exposure interact multiplicatively in this setting.[29,30] The magnitude of effect was surprisingly large in view of the range of excess risk found in asbestos-exposed workers and of the results of risk estimation.[29,30]

ACKNOWLEDGMENTS

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1989 Revisions of the US Standard Certificates and Reports

The National Center for Health Statistics (NCHS) has recently distributed to the 50 states the 1989 revisions of the US Standard Certificates and Reports of Live Birth, Death, Fetal Death, Induced Termination of Pregnancy, Marriage, and Divorce. These documents serve as models for the various states to use in developing their own forms. NCHS recommends that revised certificates and reports incorporating the 1989 changes be implemented in all states by January 1, 1989.

The US Standard Certificates and Reports were developed jointly by the NCHS and state vital registration and statistics executives. Advice was obtained from persons and organizations throughout the United States who represented users of vital statistics data and those who complete the documents. The content reflects a consensus of what needs to be collected about each vital event to serve both the legal and statistical uses of these records in the 1900s.

Among the more significant modifications made in these new revisions are:

- the addition of an Hispanic identifier to the live birth and death certificates and the fetal death and induced termination of pregnancy reports;
- changes in the birth certificate and fetal death report to obtain more detailed information about the pregnancy and its outcome; and
- some of the factors that may have improved quality and completeness of the cause of death.

Information about the revision process and copies of the standard certificates and reports can be obtained by writing or calling:

George A. Gay
Chief, Registration Methods Branch
Division of Vital Statistics, NCHS
3700 East-West Highway, Room 1-44
Hyattsville, Maryland 20782
Tel: (301) 436-8815

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Koo, L.C., Ho, J.H.-C., Saw, D. and Ho, C.-Y., "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females," International Journal of Cancer 39: 162-169, 1987.

This case-control study assessed the possible relationship of ETS and lung cancer risk in nonsmoking Hong Kong women. A total of 88 cases and 137 district- and age-matched controls was included. Housing type, as an indicator of socioeconomic status, was also considered in the matching process. 94% of the cases were histologically verified. Lifetime exposures to ETS in the home and workplace were estimated by questionnaire.

The reported RR based on husband's smoking status was 1.64 (95% CI 0.87-3.09). Numerous analyses were presented in this paper. For exposure proxies based on yes/no questions about smoking by cohabitants (husband, childhood or adulthood exposure, or others), none of the adjusted odds ratios was statistically significant at the 5% level. RRs based on husband's smoking habits, or on estimates of lifetime exposure (total years, total hours, mean hours/day, or total cigarettes/day smoked by each household smoker) did not suggest a dose-response relationship. RRs did not increase when such categories as mean hours/day, or earlier age of initial exposure, were combined with years of exposure. The authors do report increased RRs for peripheral, squamous or small-cell tumors in the middle or lower lobes.

Confounders were not discussed.

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MEASUREMENTS OF PASSIVE SMOKING AND ESTIMATES OF LUNG CANCER RISK AMONG NON-SMOKING CHINESE FEMALES

Linda C. Koo[1], John H-C. Ho[2], Daisy Saw[3] and Ching-yee Ho[1]

[1]*Dept. of Community Medicine, University of Hong Kong, Hong Kong;* [2]*Radiotherapy Dept., Baptist Hospital, Kowloon, Hong Kong; and* [3]*Institute of Pathology, Queen Elizabeth Hospital, Wylie Road, Kowloon, Hong Kong.*

Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. Relative risks based on the husband's smoking habits, or lifetime estimates of total years, total hours, mean hours/day, or total cigarettes/day smoked by each household smoker did not show dose-response results. Similarly, when such categories as mean hours/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that peripheral tumors in the middle or lower lobes, or, less strongly, squamous or small-cell tumors in the middle or lower lobes, had increasing relative risks that might indicate some association with passive smoking exposure.

Epidemiological data linking passive smoking with lung cancer among non-smokers have been controversial. Six studies (Hirayama, 1981; Trichopoulos *et al.*, 1981; Correa *et al.*, 1983; Knoth *et al.*, 1983; Miller, 1984; Garfinkel *et al.*, 1985) found significantly elevated relative risks (RR) in the range of 2.0 to 3.5 based on the smoking habits of the spouse. Five other studies (Garfinkel, 1981; Kabat and Wynder, 1984; Chan and Fung, 1982; Koo *et al.*, 1984; Wu *et al.*, 1985) two of which were conducted in Hong Kong, did not find significantly elevated RR from inhalation of sidestream tobacco smoke.

Four of these epidemiological studies (Hirayama, 1981; Trichopoulos *et al.*, 1981; Garfinkel, 1981; Chan and Fung, 1982) defined exposure solely by two questions: whether the spouse smoked (yes/no), and the number of cigarettes smoked per day by the spouse. Five other studies (Correa *et al.*, 1983; Miller, 1984; Garfinkel *et al.*, 1985; Kabat and Wynder, 1984; Wu *et al.*, 1985) also included questions about whether involuntary smoke exposure had occurred at work (yes/no), and/or whether the parents has smoked (yes/no). Such data seem rather crude indices of exposure, providing only very indirect information on the degree and amount of exposure. Furthermore, although spouse(s), parents, or co-workers might have smoked, the actual degree of contact of the non-smoker with these smokers could have been very low, or even nil (Friedman *et al.*, 1983). In our detailed studies (Koo *et al.*, 1983, 1984) of passive smoking exposures, smoking parents or spouses were sometimes recalled as inflicting little or no exposure on the subject. In those cases where, for example, the husband smoked but lived separated from the wife, then our study counted such wives as unexposed subjects. Among our never-smoked subjects, this was found to be true for 3 cases and 3 controls.

In order to assess the possible causal relationship of passive smoking to lung cancer risk, data from detailed life-history exposures that were elicited in intensive 1.5- to 2-hr tape-recorded interviews of never-smoked female lung cancer cases and district controls have been analyzed. Emphasis is placed on the consistency of the data, the strengths of the RR, and whether dose-response relationships were present.

This study of the effects of passive smoking is particularly pertinent to Hong Kong because it is one of the most crowded urban environments in the world. Its urban density averages 28,000 inhabitants/km^2, with only 8 m^2 of available living space per person.

MATERIAL AND METHODS

From 1981-3, 88 never-smoked female lung cancer patients and 137 never-smoked female district controls were interviewed as part of a larger retrospective study of female lung cancer in Hong Kong covering 200 cases and 200 controls. In the original study, patients were matched with an equal number of healthy controls by age (±5 years), district of residence (N=34), and housing type (public or private housing), the latter being an indication of socio-economic status. Details of subject selection, lung cancer histological typing, and method of conducting the interviews have been discussed elsewhere (Koo *et al.*, 1983, 1984). Never-smoked subjects were defined as those who had smoked less than 20 cigarettes in the past. All data on passive smoking exposures were double-checked with other data elicited in the life-history interviews, especially residential patterns since birth (*i.e.* where they lived, type of housing, number of rooms, number of co-habitants, etc.), occupations, and marital life to reduce errors in estimating exposure levels.

Among the never-smoked subjects, the mean age of the patients was 57.8 (SD 10.81) and that for the controls was 59.3 (SD 9.94). This sample included 60 who were widows and 3 who had never married; none had married more than once.

In the design of the interviews, separate data were collected to take into account that within the life-histories of the subjects, sidestream tobacco smoke could originate from: (a) different people who smoked in the presence of the subject; (b) different places frequented by the subject; and (c) different types of tobacco. Persons who smoked included related and unrelated members of the household, and even co-habitants who shared an apartment unit (if their tobacco smoke was noticed by the subject). It was difficult to quantify exposure levels from places that could have varying daily amounts of environmental tobacco smoke and were occasionally visited by the subject such as cinemas, while playing majong, or in transport vehicles. This analysis will only take into account exposures that remained relatively regular during the lifetimes of the subjects *i.e.* from exposures at home and the workplace(s). Among our subjects, tobacco smoke mostly originated from cigarettes smoked by household members, and from pipes (water and regular) smoked by parents or in-laws.

In addition to data based on the husband's smoking habits, 4 other measurements of passive smoking were evaluated: (a) total years of exposure, (b) total hours of exposure, (c) mean hours/day of exposure, and (d) total cigarettes per day smoked by each household member weighed by their years of exposure. These measures should be a more accurate reflection of past lifetime exposures than simple questions based on whether the spouse or parents smoked (yes/no), or whether environmental tobacco smoke was encountered in the workplace (yes/no).

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The total years of exposure were derived from adding the years during which tobacco exposure occurred in the home or workplace. Exposures of 6 or more months were rounded off to the next year. In the home environment, household smokers were only counted if the subject recalled that they had smoked in her presence. Where exposure was concurrent, as in the case of both parents smoking, or exposure occurring at the home and workplace, then the years were *not* added.

The total hours of exposure were calculated by multiplying the average hours/day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. Each of these sources of exposure was then added together for each subject. The hours were not added for exposure to simultaneous smokers. For example, a husband and son smoking at the same time for 1 hr would only be counted as 1 hr.

The mean hours/day of exposure were derived by adding the hours/day of home and workplace exposures and dividing this figure by the age of the subject. This figure approximates the average number of hours of exposure per day experienced by the subject, spread over her lifetime.

A weighted average of the total cigarettes per day smoked by each household member was calculated from the summation of the usual number of cigarettes smoked throughout the day by each household member multiplied by the years that each lived with the subject, divided by the total years during which cigarette exposure had occurred in the home. This figure may give a better indication of the intensity of cigarette exposure in the home than one simply based on the number of cigarettes smoked per day by the husband, because it accounts for other household smokers and the years that the subject was exposed to each smoker. This figure excluded exposure from pipe smoking and the cigarette consumption levels of co-workers because of difficulties in quantifying those amounts.

Of the 88 patients, 83 were typed histologically. Among the remaining 5 cases, biopsy or cytologic materials revealed that malignant cells were present, but they were too undifferentiated or unspecified for categorization by cell type. Chest radiographs were examined for all cases, and the site of the primary lung tumor was classified by its location in the bronchial tree, and whether it was centrally or peripherally situated. In this analysis, the lingula was classified as equivalent to the middle lobe, and peripheral tumors were defined as those located beyond the segmental bronchus.

Statistical analyses included the calculation of RR as the crude or adjusted odds ratio and tests for trend (Breslow and Day, 1980). Adjusted odds ratios were estimated by the use of a conditional logistic regression package, PECAN, (Lubin, 1981) which was based on N:M matching by strata defined by district (N = 34) and housing type (public or private). To take into account the effects of potential confounders which affected the RR estimates, adjustments were made for age (< 50, 50-69, 70+), any formal schooling (yes/no), number of live births, and years since exposure to cigarette smoke had ceased in the home or workplace. The exact values were used for the last two variables. Because the resulting large numbers of matching strata in the adjusted odds ratios may lead to unstable results, both crude and adjusted RR were presented for all risk analyses. The Mantel-Haenszel test for trend was performed on all the crude odds ratios using the midpoint of each interval, whereas the trend test of the logistic parameters was based on each variable as a continuous exposure factor.

RESULTS

To allow comparison of the results of this study with those done elsewhere, exposures based on the husband's cigarette smoking habits were analyzed for the ever-married women (Table I). In response to the question of whether the husband had smoked cigarettes in the presence of the wife, the crude and adjusted RR were both a non-significant 1.6. RR for the usual number of cigarettes smoked per day by the husband did not indicate increasing risk with higher smoking levels, and the trend tests for the crude ($p = 0.10$) and adjusted ($p = 0.43$) RR were not significant.

Likewise, when the data were analyzed in terms of cigarette smoke exposure during childhood/adulthood, or by the number of smoking co-habitants, as in the study of Sandler *et al.* (1985) (Table II), no consistent pattern emerged. RR at the higher levels of exposure, *i.e.*, both childhood and adulthood, or 2+ smoking co-habitants, were found to be lower than those at lower levels of exposure.

Lifetime exposure measurements

When the crude and adjusted odds ratios were calculated for the 4 lifetime exposure measurements, the RR for the intermediate exposure levels of mean hours/day (1.94 and 4.10), and cigarettes/day (1.57 and 2.56) were significant (Table III). However, with the exception of total years, all of the RR (0.9-1.4) at the high exposures were below those of low or intermediate levels. Even for total years, the Mantel-Haenszel linear trend test ($p = 0.55$) for the crude RR, and the trend test for the logistic adjusted parameters ($p = 0.23$) indicated that the pattern was insignificant.

When the crude and adjusted RR are compared (Fig. 1), the adjusted RR for these measurements showed RR fluctuating between wider ranges of 1.0 to 4.1, yet both lacked evidence of a consistent dose-response pattern.

Intensity

As a measure of intensity, RR were calculated to see whether there was a direct relationship between increasing years and mean hours/day of exposure in a 2 × 2 table (Table IV). Starting with the top left-hand square which was the group with the lowest exposure levels, one would expect RR to be higher in all the other squares, especially the one at the lower right, because it had the highest years and mean hours/day of exposure. However, the crude RR at this highest intensity level was only 1.07, and the category with the lowest intensity values (top left) had the highest adjusted RR of any of the other groups. A similar pattern emerged if total hours or cigarettes/day were substituted for mean hours in this analysis.

Age of initial exposure

We had previously found no difference in the age at which passive exposure had started (Koo *et al.*, 1984). To see whether earlier age of initial exposure combined with higher years of exposure were related with increasing risk, RR were calculated for cigarette exposures in a 2 × 2 table (Table V). Again, we did not see any pattern suggesting a dose-response relationship. The top left square with the least years of exposure and older age at initial exposure had the highest crude and adjusted RR. Similar results were obtained if the years and age of exposure included all types of environmental tobacco smoke, *i.e.* from cigarettes and pipe.

Histological type

The cases were divided into two groups, those with squamous or small-cell lung tumors, and those with adenocarcinoma or large-cell lung tumors. This division was made because the former group was previously found in Hong Kong to be more related to active smoking than the latter (Koo *et al.*, 1985). Five cases with mixed cell types and 5 with unspecified cell types were excluded from the analysis.

Although none of the crude or adjusted RR or trends by histology were found to be significant, it can be observed that a dose-response pattern seemed to be more apparent among

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TABLE I - HUSBAND'S CIGARETTE SMOKING HABITS AND RR FOR LUNG CANCER AMONG EVER-MARRIED WOMEN

Exposure	Number of cases/ number of controls	Crude RR (95% CI)	Adjusted RR[1] (95% CI)
Husband ever smoked?[2]			
No	35/70	1.00	1.00
Yes	51/66	1.55 (0.94, 3.08)	1.64 (0.87, 3.09)
Cigarettes/day smoked by husband			
0	32/67	1.00	1.00
1-10	17/15	2.37 (1.03, 5.91)	2.33 (0.92, 5.92)
11-20	25/35	1.50 (0.87, 3.64)	1.74 (0.81, 3.75)
21+	12/19	1.32 (0.45, 2.63)	1.19 (0.46, 3.03)

[1]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.–[2]Husband smoked in the presence of the wife. 3 cases and 3 controls were not exposed to the cigarettes of their husband.

TABLE II - RR FOR LUNG CANCER FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE

Exposure	Number of cases/ number of controls	Crude RR[1] (95% CI)	Adjusted RR[2] (95% CI)
By period in life			
No exposure	27/49	1.00	1.00
Children only[3]	2/3	1.21 (—)	2.07 (0.51, 95.17)
Adulthood only[4]	57/77	1.34 (0.84, 3.01)	1.68 (0.62, 5.45)
Both childhood + adulthood	2/8	0.45 (0.11, 3.32)	0.64 (0.57, 5.85)
By number of smoking co-habitants[5]			
None	27/49	1.00	1.00
1	48/68	1.28 (0.82, 3.25)	1.73 (0.57, 6.35)
2+	13/20	1.18 (0.57, 3.65)	1.35 (0.64, 5.03)

[1]Crude odds ratio.–[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.–[3]From one or both parents.–[4]From spouse, in-laws, children, or other co-habitants.–[5] From spouse, parents, in-laws, children, or other co-habitants who smoked at home in the presence of the subject.

TABLE III - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER

Total years				Hours/day			
Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)	Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)
0	22/40	1.00	1.00	0	22/40	1.00	1.00
1-19	20/28	1.30 (0.63, 3.68)	1.95 (0.72, 5.31)	<1	15/29	0.94 (0.41, 2.63)	1.05 (0.37, 2.94)
20-34	24/39	1.12 (0.59, 3.06)	1.36 (0.55, 3.36)	<2	33/31	1.94 (1.24, 6.74)	4.10 (1.59, 10.61)
35+	22/30	1.33 (0.79, 4.44)	2.26 (0.90, 5.67)	2+	18/37	0.88 (0.42, 2.42)	1.00 (0.39, 2.58)
Total hours (in hundreds)				**Cigarettes/day[3]**			
Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)	Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)
0	22/40	1.00	1.00	0	25/48	1.00	1.00
1-10	25/38	1.20 (0.60, 3.67)	1.68 (0.64, 4.45)	1-10	13/16	1.56 (0.74, 4.96)	1.83 (0.65, 5.11)
101-200	23/27	1.55 (0.88, 5.53)	2.28 (0.91, 5.72)	11-20	27/33	1.57 (1.00, 4.99)	2.56 (1.06, 6.19)
201+	18/32	1.02 (0.54, 3.47)	1.42 (0.56, 3.62)	21+	23/40	1.10 (0.51, 2.47)	1.21 (0.51, 2.86)

[1]Crude odds ratio.–[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.–[3]The sum of number of cigarettes/day smoked by each household member weighted by the years of exposure from that source. Mantel-Haenszel trend analysis: Years: 0.55; hours: 0.75; hours/day: 0.70; cig/day: 0.67. Logistic adjusted trend analysis: Years: 0.23; hours: 0.98; hours/day: 0.86; cig/day: 0.63.

TABLE IV - EFFECTS OF INCREASING YEARS AND MEAN HOURS/DAY OF TOBACCO EXPOSURE

	Years of exposure			
	1-24		25+	
Mean hours per day of exposure	RR[1]	RR[2]	RR[1]	RR[2]
<1.5	1.33[3]	2.22[4] (19/26)[5]	1.47	2.13 (21/26)
≥1.5	1.02	1.21 (9/16)	1.07	1.45 (17/29)

[1]Crude odds ratio.–[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.–[3]95% CI: 1.33 (0.68, 4.00), 1.47 (0.74, 4.30), 1.02 (0.39, 3.45), 1.07 (0.57, 3.39).–[4]95% CI: 2.22 (0.79, 6.21), 2.13 (0.84, 5.43), 1.21 (0.37, 3.96), 1.45 (0.56, 3.78).–[5]Number of cases/number of controls. 22 cases and 40 controls had no exposure = RR 1.00.

TABLE V - EFFECTS OF INCREASING YEARS AND EARLIER AGE OF INITIAL EXPOSURE TO CIGARETTE SMOKE

	Years of exposure			
	1-24		25+	
Age at first exposure	RR[1]	RR[2]	RR[1]	RR[2]
≥25	1.50[3]	1.95[4] (20/25)[5]	1.50	1.67 (8/10)
≤24	1.00	1.35 (8/15)	1.25	1.86 (28/42)

[1]Crude odds ratio.–[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.–[3]95% CI: 1.50 (0.71, 3.99), 1.50 (0.47, 4.64), 1.00 (0.41, 3.42), 1.25 (0.76, 3.60).–[4]95% CI: 1.95 (0.76, 4.98), 1.67 (0.52, 5.33), 1.35 (0.30, 6.18), 1.86 (0.78, 4.46).–[5]Number of cases/number of controls. 24 cases and 45 controls had no exposure = RR 1.00.

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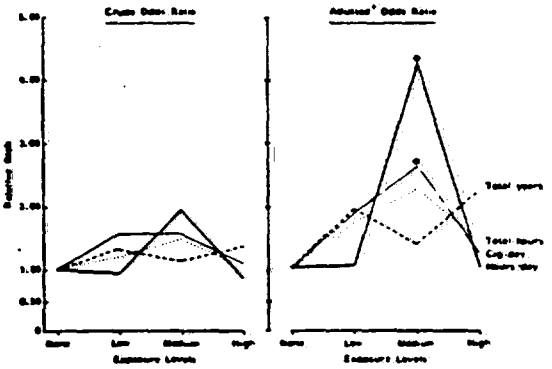

FIGURE 1 - Measurements for passive smoking and RR for lung cancer. *Adjusted for age, number of live births, schooling (+/−) and years since exposure to cigarette smoke ceased in the home or workplace. °$p \leq 0.05$.

the squamous or small-cell lung tumors than among the adenocarcinoma or large-cell types (Table VI). This was especially true for the adjusted RR in the former group, as 3 of the 4 measurements consistently indicated increasing risk with increasing exposure.

Location by lobe

Eighty of the cases had the main tumor residing in one of the lobes. The remaining 8 cases, with primary tumors in the right or left main bronchus, or in the right intermedius region, were too few for analysis. Calculations of the RR showed that none of the crude or adjusted values were significant for upper-lobe tumors (Table VII). For the middle or lower lobes, all of the adjusted RR were in the comparatively higher range of 1.9-3.5 for those with some passive exposure. Moreover, for 3 of the exposure measurements, total years, hours/day, and cigarettes/day, the confidence intervals for the crude and adjusted RR indicated some borderline significant values. However, none of the trend analyses for the lobe data came out significant.

TABLE VI - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER BY HISTOLOGICAL TYPE

	Squamous or small-cell			Adenocarcinoma or large-cell		
	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years						
0	7/40	1.00	1.00	12/40	1.00	1.00
1-26	10/46	1.24 (0.37, 5.40)	1.58 (0.37, 6.77)	17/46	2.11 (0.54, 3.74)	2.07 (0.64, 6.71)
27+	15/51	1.68 (0.47, 5.79)	1.82 (0.49, 6.80)	17/51	1.90 (0.51, 3.27)	1.43 (0.51, 4.02)
Total hours (in hundreds)						
0	7/40	1.00	1.00	12/40	1.00	1.00
1-150	12/56	1.22 (0.34, 4.71)	1.40 (0.34, 5.77)	18/56	1.07 (0.48, 3.05)	1.70 (0.55, 5.20)
151+	13/41	1.81 (0.52, 6.54)	2.04 (0.53, 7.85)	16/41	1.30 (0.59, 4.02)	1.57 (0.55, 4.49)
Hours/day						
0	7/40	1.00	1.00	12/40	1.00	1.00
<1.3	8/44	1.04 (0.31, 4.70)	1.34 (0.31, 5.84)	17/44	1.29 (0.56, 3.61)	2.19 (0.71, 6.77)
≥1.3	17/53	1.83 (0.52, 6.69)	2.01 (0.52, 7.72)	17/53	1.07 (0.49, 3.23)	1.34 (0.47, 3.82)
Cigarettes/day						
0	9/48	1.00	1.00	13/48	1.00	1.00
1-19	9/26	1.85 (0.57, 7.20)	2.02 (0.53, 7.68)	12/26	1.70 (0.77, 5.72)	2.05 (0.63, 6.72)
20+	14/62	1.20 (0.36, 3.31)	1.19 (0.36, 3.93)	19/62	1.13 (0.59, 3.57)	1.88 (0.68, 5.17)

[1]Crude odds ratio.-[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.

TABLE VII - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER BY LOBAR LOCATION

	Upper lobes			Middle or lower lobes		
	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years						
0	10/40	1.00	1.00	11/40	1.00	1.00
1-26	11/46	0.96 (0.43, 3.82)	0.98 (0.27, 3.64)	17/46	1.34 (0.86, 8.72)	3.08 (0.83, 11.38)
27+	16/51	1.25 (0.40, 2.87)	1.42 (0.46, 4.42)	15/51	1.07 (0.62, 6.15)	2.13 (0.62, 7.24)
Total hours (in hundreds)						
0	10/40	1.00	1.00	11/40	1.00	1.00
1-150	15/56	1.07 (0.30, 2.38)	1.30 (0.38, 4.50)	18/56	1.17 (0.76, 7.26)	2.37 (0.67, 8.35)
151+	12/41	1.17 (0.38, 3.01)	1.23 (0.39, 3.91)	14/41	1.24 (0.68, 7.17)	2.51 (0.72, 8.84)
Hours/day						
0	10/40	1.00	1.00	11/40	1.00	1.00
<1.3	7/44	0.64 (0.15, 1.58)	0.69 (0.18, 2.61)	17/44	1.40 (0.95, 9.51)	3.24 (0.90, 11.66)
≥1.3	20/53	1.51 (0.51, 3.70)	1.64 (0.54, 5.01)	15/53	1.03 (0.55, 5.55)	1.97 (0.57, 6.82)
Cigarettes/day						
0	10/48	1.00	1.00	12/48	1.00	1.00
1-19	10/26	1.85 (0.57, 5.39)	2.32 (0.62, 8.76)	12/26	1.85 (1.08, 10.39)	3.49 (0.98, 12.50)
20+	17/62	1.32 (0.48, 3.32)	1.79 (0.59, 5.45)	17/62	1.10 (0.61, 4.61)	1.93 (0.63, 5.95)

[1]Crude odds ratio.-[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.

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Proximal/peripheral location

Among the 85 determinable cases, 46 had peripheral tumors, and 39 proximal tumors. Although only the crude RR of 2.00 and adjusted RR of 3.52 for 1-19 cigarettes/day were slightly significant for the proximal tumors, in general, all of the crude and adjusted RR for the peripheral tumors were greater than 1.00 (Table VIII).

Histological type and location

In order to see whether any particular combination of histological type, lobe, or proximal/peripheral location of the tumor would result in stronger dose-response patterns by the 4 lifetime measurements of passive smoking, RR were analyzed for the 12 possible 1:1 combinations. We were unable to segregate the cases into any finer categories than 2 of the 3 groups because of the small resulting number of cases for analysis. Space does not allow us to present all the tables, but the best combination was that of peripheral tumors in the middle or lower lobes (Table IX). Among the RR, significant or nearly significant figures were found for the crude or adjusted RR relating to at least one of the exposure categories for each type of measurement. Moreover, the adjusted RR tended to range between the relatively high values of 6.5 to 18.7 for those with some exposure (Fig. 2), and most of these were significant or nearly significant. None of the trend tests came out significant, but this and the tendency for the higher levels of exposure to have lower RR than the low levels of exposure may have been due to the small number of cases (N=24).

Although not as apparent, squamous and small-cell lung cancers in the middle or lower lobes (Fig. 3) also seemed to show some positive association with passive smoking. There were only 18 cases with this type for analysis and none of the RR or tests for trend were found to be statistically significant (Table X). Yet it was promising to see that all the RR with some exposure were greater than 1.0. Among the highest exposure levels for the adjusted RR, values as high as 7.0 were found for total hours, and 6.2 for hours/day.

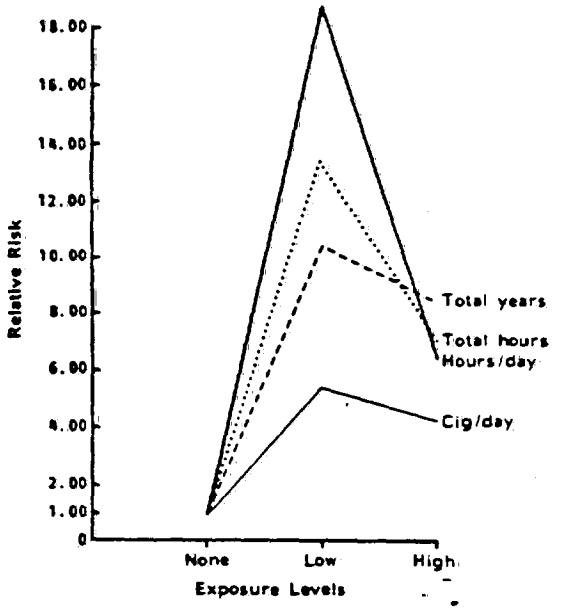

FIGURE 2 - Measurements of passive smoking and RR for peripheral lung cancers in the middle or lower lobes. Adjusted odds ratio.

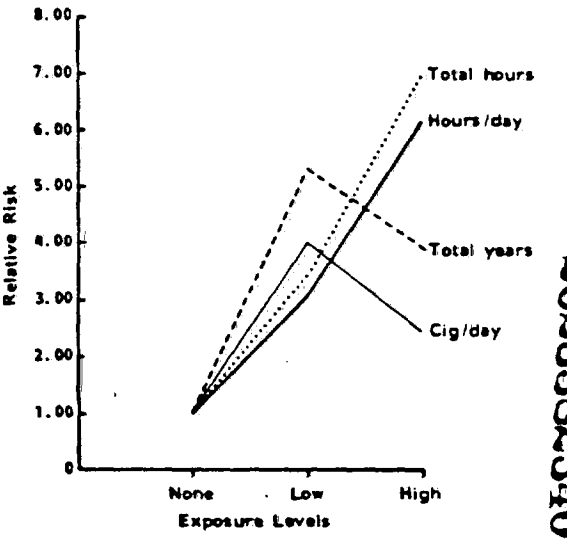

FIGURE 3 - Measurements of passive smoking and RR for squamous and small-cell lung cancer in the middle or lower lobes. Adjusted odds ratio.

DISCUSSION

For comparative purposes, the more commonly used measurements of passive smoking based on yes/no questions of whether household co-habitants (husband, childhood/adulthood, or others) had smoked, or on the number of cigarettes the husband smoked per day, were presented. Only the crude RR of 2.37 (95% CI:1.03-5.91) for husbands smoking 1-10 cigarettes/day was of borderline significance and none of the adjusted odds ratios were significant at the $\leq 5\%$ probability level. There was little indication that increasing levels of such exposure led to increased RR.

On the basis of our extensive life-history data, we were able to calculate the total years, hours, mean hours/day, and cigarettes/day to which the subjects had been exposed to tobacco smoke at home or at work. Our estimates were based on the understanding that the household composition of each subject would change as she progressed through the life-cycle of birth, childhood, adulthood, marriage, motherhood and, for 27%, widowhood. We also included exposures from each workplace at which the subject had worked for at least 3 months. In our adjusted RR, the effect of cessation of exposure to passive smoking was accounted for by putting in the years that exposure had ceased at home and/or workplace as a continuous regressor variable.

Despite such detailed accounting, we were unable to find a significant trend in the crude or adjusted RR for these 4 lifetime measurements of passive smoking. Although the RR for the intermediate level exposures of hours/day and cigarettes/day were significant, the RR at the highest levels of exposure for these two variables fell to a non-significant 1.0-1.2. In fact, the RR for the highest exposure levels for 3 out of the 4 measurements were below all of those with lower exposures, and ranged from a very weak 1.0 to 1.4. On the other hand, most of the crude and adjusted RR were greater than 1.00.

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TABLE VIII - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER BY LOCATION OF TUMOR

	Peripheral			Proximal		
	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years						
0	10/40	1.00	1.00	11/40	1.00	1.00
1–26	18/46	1.57 (0.59, 4.84)	1.52 (0.44, 5.17)	14/46	1.11 (0.50, 4.14)	2.15 (0.64, 7.19)
27+	18/51	1.41 (0.64, 4.78)	1.84 (0.62, 5.45)	14/51	1.00 (0.43, 3.51)	1.58 (0.51, 4.92)
Total hours (in hundreds)						
0	10/40	1.00	1.00	11/40	1.00	1.00
1–150	20/56	1.43 (0.63, 4.97)	1.82 (0.57, 5.85)	16/56	1.04 (0.46, 3.53)	1.86 (0.58, 5.97)
151+	16/41	1.56 (0.60, 4.71)	1.66 (0.54, 5.06)	12/41	1.06 (0.47, 4.19)	1.72 (0.54, 5.51)
Hours/day						
0	10/40	1.00	1.00	11/40	1.00	1.00
<1.3	14/44	1.27 (0.56, 4.62)	1.66 (0.52, 5.33)	13/44	1.07 (0.48, 3.94)	2.21 (0.63, 7.75)
⩾1.3	22/53	1.66 (0.66, 4.98)	1.77 (0.59, 5.32)	15/53	0.89 (0.44, 3.69)	1.59 (0.51, 4.93)
Cigarettes/day						
0	12/48	1.00	1.00	12/48	1.00	1.00
1–19	11/26	1.69 (0.73, 6.14)	1.91 (0.57, 6.35)	13/26	2.00 (0.98, 9.17)	3.52 (1.01, 12.27)
20+	23/62	1.48 (0.70, 4.34)	1.79 (0.64, 5.03)	12/62	0.77 (0.34, 2.45)	1.23 (0.42, 3.62)

[1]Crude odds ratio –[2]Adjusted for age, number of live births, schooling (+/–), and years since exposure to cigarette smoke ceased in the home or workplace.

TABLE IX - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR PERIPHERAL LUNG CANCERS IN THE MIDDLE OR LOWER LOBES

Exposure	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years			
0	4/40	1.00	1.00
1–26	10/46	2.17 (0.98, 84.95)	10.44 (0.91, 119.53)
27+	10/51	1.96 (0.88, 66.91)	8.61 (0.84, 88.21)
Total hours (in hundreds)			
0	4/40	1.00	1.00
1–150	12/56	2.14 (1.24, 110.17)	13.51 (1.16, 157.74)
151+	8/41	1.95 (0.69, 56.35)	7.02 (0.64, 76.93)
Hours/day			
0	4/40	1.00	1.00
<1.3	11/44	2.50 (1.71, 160.18)	18.70 (1.53, 228.03)
⩾1.3	9/53	1.70 (0.62, 49.89)	6.49 (0.60, 70.37)
Cigarettes/day			
0	6/48	1.00	1.00
1–19	6/26	1.85 (0.95, 24.36)	5.53 (0.79, 38.86)
20+	12/62	1.55 (0.74, 13.14)	4.16 (0.77, 22.55)

[1]Crude odds ratio –[2]Adjusted for age, number of live births, schooling (+/–), and years since exposure to cigarette smoke ceased in the *home* or workplace.
Mantel-Haenszel trend analysis: Years: 0.15; hours: 0.16; hours/day: 0.14; cig/day: 0.29.
Logistic adjusted trend analysis: Years: 0.15; hours: 0.66; hours/day: 0.53; cig/day: 0.22.

TABLE X - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR SQUAMOUS AND SMALL-CELL LUNG CANCERS IN THE MIDDLE OR LOWER LOBES

Exposure	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years			
0	3/40	1.00	1.00
1–26	7/46	2.03 (0.52, 44.44)	5.29 (0.51, 54.71)
27+	8/51	2.09 (0.42, 33.01)	3.97 (0.41, 38.22)
Total hours (in hundreds)			
0	3/40	1.00	1.00
1–150	6/56	1.43 (0.35, 29.32)	3.44 (0.35, 34.17)
151+	9/41	2.93 (0.59, 46.98)	7.01 (0.64, 76.60)
Hours/day			
0	3/40	1.00	1.00
<1.3	4/44	1.21 (0.30, 29.64)	3.05 (0.28, 33.14)
⩾1.3	11/53	2.77 (0.57, 44.05)	6.16 (0.59, 64.48)
Cigarettes/day			
0	4/48	1.00	1.00
1–19	5/26	2.31 (0.58, 23.25)	3.97 (0.54, 29.20)
20+	9/62	1.74 (0.44, 11.87)	2.58 (0.42, 15.93)

[1]Crude odds ratio.–[2]Adjusted for age, number of live births, schooling (+/–), and years since exposure to cigarette smoke ceased in the home or workplace.
Mantel-Haenszel *trend* analysis: Years: 0.23; hours: 0.20; hours/day: 0.26; cig/day: 0.20.
Logistic adjusted trend analysis: Years: 0.71; hours: 0.76; hours/day: 0.70; cig/day: 0.78.

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Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cigarettes/day) by mean hours/day of exposure, also did not indicate a dose-response relationship. Likewise, the analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher RR. It was troubling to find that in both types of analysis, the RR for the lowest amounts of exposure were among the highest values.

Dalhamn *et al.* (1968) noted from their study of the retention of cigarette smoke components in human lung, that water-insoluble volatile compounds and particulate matter from cigarettes tended to be deposited primarily in the deeper parts of the respiratory tree. Since adenocarcinoma is predominant among non-smoker lung cancer cases (59% of our typed cases) and it is generally a peripheral tumor, we wanted to see whether the passive smoking measurements would exhibit a more consistent pattern among the adenocarcinoma and large-cell types, and/or among the peripheral tumors. In general, the peripheral tumors as a group showed stronger dose-response results than the adenocarcinomas.

The RR for total years, hours, and hours/day measurements of squamous and small-cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted RR for adenocarcinoma or large-cell lung cancers. This association of histology with passive smoking is also suggested from previous studies by Trichopoulos *et al.* (1981) and Correa *et al.* (1983).

Analysis of the cases by the lobe location of the tumor was done to see whether the primary tumor resided more frequently in the upper lobes than in the lower lobes. This is because it is known that when dust is inhaled, it first enters the upper lobes where much of it is deposited, and then travels down to the lower lobes (Time, 1980). Furthermore, it has been observed (J.H-C. Ho, personal observation) that up to half of the Hong Kong adult population have radiologically evident scars on the upper lobes of their lungs. Most of these scars are due to previous tuberculosis infection. Since "lung cancer is more common in the scarred and chronically diseased lung" (Stone *et al.*, 1978), we were interested to see whether the lobe data would substantiate any of these possibilities. In fact, 37 of the lung cancers were found in the upper lobes, and 43 in the middle or lower lobes. The results from the RR estimates from the 4 types of measurements did not show the upper lobes to be more sensitive to environmental tobacco smoke.

Wynder and Goodman (1983) suggested that lung cancer in non-smokers was more likely to occur in the periphery of the lung. This was found in our study, as 54% of the determinable cases had peripheral tumors *vs.* 46% with proximal tumors. Moreover, the pattern of RR with the various measurements of passive smoking indicated that peripheral tumors seemed to exhibit better dose-response RR than proximal tumors.

When the RR were calculated for the 12 possible 1:1 combinations resulting from histological type, location by lobe, or proximal/peripheral tumors, the highest RR were found for peripheral tumors in the middle or lower lobes. Significant adjusted RR as high as 18.7 were found for some of these measurements. Although RR at the lower doses tended to be higher than that for the higher doses, the data were consistent in that all the RR for those with some exposure were much greater than 1.0, and the adjusted RR for at least one of the RR for each type of measurement was statistically significant or nearly significant.

The RR analysis for squamous and small-cell lung cancers in the middle or lower lobes also appeared somewhat better than the others, with total hours and hours/day measurements showing some dose-response pattern. With the above two combined analyses showing some promise, perhaps the best RR would have been obtained if analysis had been done with squamous or small-cell peripheral tumors in the middle or lower lobes. We were unable to do these calculations because only 8 cases fitted into this category.

Actually, the finding of a possible risk of squamous and small-cell tumors in the middle or lower lobes was somewhat unexpected, given that dust particles tend to adhere to the upper lobes, and tuberculosis usually affects the upper lobes. To see whether calcified foci or fibrosis in the upper lobes could account for the higher RR in the middle or lower lobes because the previous presence of such lesions might disturb the expected distribution of inhaled particulate or gaseous matter, most of the chest radiographs of cases with squamous and small-cell lung tumors were re-examined. No significant difference was found in the proportion of positive cases with upper lobe *vs.* lower lobe tumors.

In our analysis of *all* never-smoked cases, the lack of a dose-response pattern, and an almost consistent drop in the RR at the highest doses of exposure would seem to lend little, or only weak support for the passive smoking linkage with lung cancer for women in Hong Kong. This might be due to the fact that it has been estimated (Rylander *et al.*, 1983) that the non-smoker exposed to environmental tobacco smoke receives about 1% of the active smoker's dose of tobacco smoke based on cotinine levels in the body, and this is roughly equivalent to the tobacco smoke of 0.1-1.0 cigarette inhaled by an active smoker in a day. Moreover, a 15- to 17-year longitudinal study of 97 non-smoking females in Holland did not find an association between passive smoking exposure and pulmonary function decline (Brunekreef *et al.*, 1985). Thus the effects of passive smoking might be so weak that they are easily overshadowed by other environmental factors such as diet or exposure to inhaled gaseous/particulate matter from other sources in the home or the workplace.

When the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small-cell tumors in the same lobes, exhibited better RR patterns for passive smoking in terms of consistency, strength, and dose-response. We are not sure whether this proclivity for passive-smoking-related lung tumors to reside in the middle or lower lobes might be due to the fact that the lower lobes have more bronchial cells at risk than the upper lobes, or whether the size, weight, or composition of gaseous or particulate matter from passive smoking may favor its adherence to the peripheral areas and the lower lobes. Nevertheless, the overall proportion of lung tumors in the middle or lower lobes among our 88 cases ranged from 27% for the peripheral tumors to 20% for the squamous or small-cell tumors. Thus, the majority of lung cancers among our non-smoking population were probably due to some factor(s) which yet remain to be identified.

The results from this study, showing a weak effect of passive smoking on the risk of lung cancer among never-smoked Hong Kong Chinese women, must be interpreted cautiously, since it was based on only 88 cases and 137 controls. With this sample size, RR less than approximately 1.4 would be difficult to detect with 95% power and at the 5% level of significance. This problem was even greater when the cases were stratified by histological type and location of the primary tumor. However, these data seem consistent with the findings from other epidemiological, biochemical, and physiological studies in showing higher risks for squamous-cell tumors in the peripheral areas of the lung. Confirmation of these findings from other studies is therefore needed.

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out of the fieldwork. We are also indebted to the US National Cancer Institute's Fogarty International Center for sponsoring a 4-month Visiting Scientist post in the Epidemiology and Biostatistics Program, which was invaluable in the analysis of the data. The secretarial assistance of Mrs. T. Lam, Ms. A. Chow and Ms. M. Chi, and the graphics work of the Medical Illustration Unit, are gratefully acknowledged.

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Lam, T.H., Kung, I.T.M., Wong, C.M., Lam, W.K., Kleevens, J.W.L., Saw, D., Hsu, C., Seneviratne, S., Lam, S.Y., Lo, K.K. and Chan, W.C., "Smoking, Passive Smoking and Histological Types in Lung Cancer in Hong Kong Chinese Women," British Journal of Cancer 56(5): 673-678, 1987.

In this case-control study of Chinese women in Hong Kong, 445 histologically confirmed cases and 445 age-matched neighborhood controls were compared. This study is hampered by the poor method used to select controls: a researcher simply visited houses near the address of the case until a woman of the correct age was found. Statistically significantly elevated RRs were reported for all major cell types with active smoking; significant trends between RR and amount of tobacco smoked daily were also reported.

For nonsmoking women, a RR of 1.65 (95% CI 1.16-2.35) for having a smoking husband was reported; a significant trend between RR and amount smoked daily by the husband was claimed. When broken down by cell types, an elevated risk was reported only for adenocarcinoma (RR = 2.12, 95% CI 1.32-3.39). A significant trend between RR and amount smoked daily by the husband was also reported.

No potential confounders were considered.

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Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women

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T.H. Lam[1], I.T.M. Kung[2], C.M. Wong[1], W.K. Lam[3], J.W.L. Kleevens[1], D. Saw[4], C. [illegible], S. Seneviratne[5], S.Y. Lam[2], K.K. Lo[5] & W.C. Chan[4]

Departments of [1]Community Medicine, [2]Pathology, [3]Medicine, University of Hong Kong, [4] Queen Elizabeth Hospital and [5]Kowloon Hospital, Hong Kong.

Summary In a case control study in Hong Kong, 445 cases of Chinese female lung cancer patients all confirmed pathologically were compared with 445 Chinese female healthy neighbourhood controls matched for age. The predominant histological type was adenocarcinoma (47.2%). The relative risk (RR) in ever-smokers was 3.81 ($P<0.001$, 95% CI = 2.86, 5.08). The RRs were statistically significantly raised for all major cell types with significant trends between RR and amount of tobacco smoked daily. Among never smoking women, RR for passive smoking due to a smoking husband was 1.65 ($P<0.01$, 95% CI = 1.16, 2.35) with a significant trend between RR and amount smoked daily by the husband. When broken down by cell types, the numbers were substantial only for adenocarcinoma (RR = 2.12, $P<0.01$, 95% CI = 1.32, 3.39) with a significant trend between RR and amount smoked daily by the husband. The results suggest that passive smoking is a risk factor for lung cancer, particularly adenocarcinoma in Hong Kong Chinese women who never smoked.

In Hong Kong, lung cancer is the major cause of death in both males and females. In 1985, there were 2,223 deaths attributed to malignant neoplasms of the trachea, bronchus and lung (ICD 9th Revision Code 162) which accounted for 29.5% of deaths due to all forms of cancer; 1,457 in males, (31.7%) and 766 (26.0%) *in females* (Director of Medical & Health Services of Hong Kong, 1986).

On a world scale, male lung cancer death rates are not particularly high in Hong Kong. However, the female rates are among the highest in the world with an age-standardized incidence rate of 23.4 per 100,000 in 1974–1977 (Waterhouse *et al.*, 1982), resulting in an unusually low male to female ratio. The most common cell type in males is squamous cell carcinoma (33.3%) and in females, adenocarcinoma (49.6%) (Kung *et al.*, 1984). A case control study in 1976–1977 confirmed the relationship between lung cancer and smoking in males, but in females about half the lung cancer patients were found to be non-smokers, of whom two thirds were suffering from adenocarcinoma (Chan *et al.*, 1979). Further studies on passive smoking and other risk factors have been carried out in Hong Kong but they failed to throw much light on the causes of lung cancer in never smoking females (Chan & Fung, 1982; Lam *et al.*, 1983; Koo *et al.*, 1984; Koo *et al.*, 1985).

The present study aimed to answer the following questions:

1. Is smoking a major risk factor for lung cancer in Hong Kong Chinese women and if so, what is the relationship between smoking and the histological types of lung cancer?
2. Is passive smoking due to a smoking husband a risk factor for lung cancer in Hong Kong Chinese women who have never smoked themselves and if so, what is the relationship between passive smoking and histological type?

Materials and methods

A standardized structured questionnaire was designed for interviewing both cases and controls. The questions on smoking habit were modified from those of the Questionnaire on Respiratory Symptoms of the Medical Research Council (1966). The subject was asked whether she smoked, or had ever smoked as much as one cigarette a day (or one cigar a week or one ounce of tobacco a month), for one year. If the reply was negative, we checked again by asking a further question on whether she had ever smoked any amount of any type of tobacco at all in her whole life up to the time of the interview. Because of very few positive responses to this additional question, we were satisfied that under-reporting of the smoking habit was not a major problem. As elsewhere, an ever-smoker was defined as one who had ever smoked as much as one cigarette a day or equivalent for as long as a year. If a subject had ever smoked, questions on the type of tobacco and amount usually smoked per day, age when smoking started regularly and for ex-smokers only, age when smoking was given up permanently, were asked. A never-smoker was defined as one who had never smoked as much as one cigarette a day or equivalent for the duration of one year.

The smoking history of the subject's husband was ascertained in similar way if the subject was married. The same definitions of ever- and never-smoker were used for the husband. A women was considered exposed to her husband's tobacco smoke if she had lived together with her smoking husband in the same household for at least one year continuously. If the husband was an ever-smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained.

The questionnaire also contained sections on demographic and other variables. It was tested, amended and finalised before use in the study. Eight government or government-assisted hospitals in which most of the lung cancer patients were treated in Hong Kong granted us permission for interviewing of patients.

During the interviewing phase of the study, we intended to include all lung cancer patients of the eight hospitals whose diagnosis was based on strong clinico-radiological criteria and with histological and/or cytological confirmation. Patients admitted to these hospitals who were suspected by the hospital clinicians to have lung cancer or who had already been given a confirmed diagnosis of lung cancer were interviewed as soon as possible after their admission, before their physical condition deteriorated. Only patients with their diagnosis confirmed by a pathologist's report(s)

Correspondence: T.H. Lam, Department of Community Medicine, University of Hong Kong, Li Shu Fan Building, 5 Sassoon Road, Hong Kong.

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were included as cases. Patients with a provisional diagnosis were considered only as suspected cases and they were followed up after being interviewed. Only those who subsequently had a pathology report confirming the diagnosis of lung cancer were included. Those without such confirmation were not included in the present study. The pathology report was required to state unambiguously that the patient was suffering from lung cancer before it was accepted. Information on cell type if available, was noted. Cases without information on cell type or unclassified because of undifferentiated tumours were grouped under 'others and unclassified'. The few patients with rare tumours such as carcinoid were excluded. Because these hospitals were visited frequently by the interviwers so that all eligible patients would be interviewed other than the few patients who declined to co-operate or were too ill, we believed that we had missed only very few eligible patients.

For each case, a healthy female control matched for age (±5 years) living in the same neighbourhood of the case was interviewed. The procedure of control selection was that when a patient was interviewed and included as a pathologically confirmed case, the age and address of the case was noted. The interviewer then went to the address of the case and started to visit the nearest neighbourhood addresses until she found a woman who appeared healthy and was within 5 years of age of the case. A few questions on present state of health were asked to check that the subject was indeed healthy and if so, the same questionnaire was completed. Thus the controls were matched for sex, age and place of residence.

Interviewing took place between 1983 and 1986, and involved experienced female interviewers. The language used was mainly Cantonese. Each interview took about 30 min to complete. Cooperation of interviewees was good and non-response was rare (~1%).

The present paper presents the findings on the smoking history of the subjects themselves and for the never-smokers, the history of passive smoking due to a smoking husband. Four hundred and forty-five cases and 445 controls were included. Relative risks (RR) and 95% confidence intervals (CI) (Woolf's logit limits) were calculated for each level of risk factor. Fisher's exact test (two-sided) was used to check whether the RR was significantly different from unity. χ^2 test for linear trend was performed to test whether there was a trend between RR and the levels of exposure (Breslow & Day, 1980). Subjects with missing data were excluded from the analysis.

We carried out separate analysis on cigarette only or on all forms of tobacco, by including single (never-married) women or by excluding them, by amount smoked daily, by duration of exposure or by total amount of exposure (amount smoked daily multiplied by duration). Because of the similar results and space limitation, only the results on all forms of tobacco, with single women included and by amount smoked daily are reported in the present paper.

Results

Thirty four percent of the cases were confirmed primarily by bronchial or lung biopsy, 12% by lung resection, 8% by lymph node biopsy, 9% by pleural biopsy, 17% by sputum cytology, 12% by pleural fluid cytology, 6% by bronchial aspirate, brushing, etc., 0.2% by autopsy and 2% by other methods.

The distribution of the cases by cell type and by smoking history is shown in Table I.

The distribution of cell types differed somewhat according to the basis of diagnosis. Resection and pleural biopsy yielded 70% adenocarcinoma while other methods resulted in 30–35% adenocarcinoma. Bronchial and lung biopsy resulted in ~30% while other methods resulted in about 10% squamous cell carcinoma.

A comparison of cases and controls by age and place of residence confirmed that they were similar in the two matching variables. The mean age of the cases was 65.6 years (s.d. 11.2 years) and that of the controls was 65.3 years (s.d. 10.9 years). Comparison by other demographic variables showed that the cases and controls were comparable in place of birth, duration of stay in Hong Kong, level of education, marital status, and husband's occupation. Thus, by matching the controls with the cases by age and residence, a high degree of comparability was achieved with regard to many other demographic variables.

Table II shows the Relative Risks (RR) by history of ever-smoking and cell types. Among the cases for all cell types combined, 54.5% were ever-smokers and 45.5% were never-smokers whereas among the controls, the corresponding percentages were 23.9% and 76.1%. The overall RR for ever-smoking was 3.81. The RRs were significantly raised in each of the 4 cell types, being highest for small cell carcinoma (RR = 12.00), followed by squamous cell carcinoma (RR = 8.10), large cell carcinoma (RR = 6.93) and adenocarcinoma (RR = 1.87).

Table III shows the RR by amount of tobacco smoked daily by the subjects. Significant trends were found for all cell types combined and for each of the 4 cell types.

Table IV shows the RR for passive smoking due to a smoking husband and cell types. Single (never married) women were treated as non-exposed to husband's smoking. The RR was 1.65 for all cell types combined. For individual cell types, the numbers were too small to be statistically significant except for adenocarcinoma, with a RR of 2.12. Table V shows the RR for passive smoking by amount smoked daily by the husband. Significant trends were found for all cell types combined and for adenocarcinoma only. No significant RR or trend was found for other cell types and the details are not reported here. Because similar results were obtained when single women were excluded, these are also not reported. It should be noted that the proportions of single (never-married) women in the cases and controls was 6.8% and 5.2% respectively.

Table I Distribution of cell type by smoking habit of cases and comparison with Kung *et al's* (1984) series

	Squamous cell carcinoma		*Small cell carcinoma*		*Adenocarcinoma*		*Large cell carcinoma*		*Others and unclassified*		*Total*	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Present Series												
Never smoker	28	30.4	9	17.6	131	62.4	9	45.0	25	34.7	202	45.4
Ever smoker	63	68.5	42	82.4	79	37.6	11	55.0	47	65.3	242	54.4
Missing data	1	1.1	—	—	—	—	—	—	—	—	1	0.2
Total	92	100.0	51	100.0	210	100.0	20	100.0	72	100.0	445	100.0
(% of 444 cases)	(20.7)		(11.5)		(47.2)		(4.5)		(16.2)		(100.0)	
Series of Kung *et al.* (1984)	77		43		169		34		18		341	
(% of 341 cases)	(22.6)		(12.6)		(49.6)		(10.0)		(5.3)		(100.0)	

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Table II History of ever smoking (all forms of tobacco) in 444 cases and 443 controls by cell types

Cell type	Smoking history of subjects: Case No	Case Yes	Control No	Control Yes	Relative risk (& 95% CI)	P
Squamous cell carcinoma	28	63	72	20	8.10 (4.16, 15.77)	<0.001
Small cell carcinoma	9	42	36	14	12.00 (4.65, 30.98)	<0.001
Adenocarcinoma	131	79	158	51	1.87 (1.23, 2.85)	<0.01
Large cell carcinoma	9	11	17	3	6.93 (1.53, 31.38)	<0.05
Others and unclassified	25	47	54	18	5.64 (2.71, 11.60)	<0.001
All cell types	202	242	337	106	3.81 (2.86, 5.08)	<0.001

Notes: For each cell type, the cases were compared with their matched controls. One case and 2 controls with missing data on smoking were excluded.

Table III Amount smoked daily (all forms of tobacco) in cases and controls by cell types

Amount smoked daily by subjects	All cell types: Case	Control	Relative risk (& 95% CI)	P	Squamous cell carcinoma: Case	Control	Relative risk (& 95% CI)	P
Nil	202	337	1		28	72	1	
1–10	101	63	2.67 (1.87, 3.83)	<0.001	23	11	5.38 (2.32, 12.46)	<0.001
11–20	90	28	5.36 (3.39, 8.48)	<0.001	28	6	12.00 (4.49, 32.10)	<0.001
21+	39	9	7.23 (3.43, 15.24)	<0.001	10	1	25.71 (3.14, 210.30)	<0.001
Total	432	437			89	90		
Test for trend	$\chi^2 = 89.5$, $P < 0.001$				$\chi^2 = 41.96$, $P < 0.001$			

Amount smoked daily by subjects	Small cell carcinoma: Case	Control	Relative risk (& 95% CI)	P	Adenocarcinoma: Case	Control	Relative risk (& 95% CI)	P
Nil	9	36	1		131	158	1	
1–10	16	10	6.4 (2.18, 18.77)	<0.001	36	29	1.50 (0.87, 2.57)	>0.05
11–20	14	4	14.0 (3.70, 52.92)	<0.001	27	14	2.33 (1.17, 4.62)	<0.05
21+	11	0	–	<0.001	9	5	2.17 (0.71, 6.64)	>0.05
Total	50	50			203	206		
Test for trend	$\chi^2 = 32.61$, $P < 0.001$				$\chi^2 = 8.04$, $P < 0.01$			

Amount smoked daily by subjects	Large cell carcinoma: Case	Control	Relative risk (& 95% CI)	P	Others and unclassified: Case	Control	Relative risk (& 95% CI)	P
Nil	9	17	1		25	54	1	
1–10	6	3	3.78 (0.76, 18.79)	>0.05	20	10	4.32 (1.77, 10.57)	<0.01
11–20	4	0	–	<0.05	17	4	9.18 (2.80, 30.11)	<0.001
21+	1	0	–	>0.05	8	3	5.76 (1.41, 23.57)	<0.05
Total	20	20			70	71		
Test for trend	$\chi^2 = 8.17$, $P < 0.01$				$\chi^2 = 19.86$, $P < 0.001$			

Notes: Subjects with missing data on amount smoked daily were excluded.

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the relative risks for adenocarcinoma found in other Hong Kong studies: 1.59 (Chan *et al.*, 1979), 1.80 (Lam *et al.*, 1983), 1.88 (Koo *et al.*, 1985) and 2.1 (Lam, 1985). The significant trend observed for adenocarcinoma provides further evidence that smoking is also a risk factor for this cell type.

The association between histological types and smoking was reviewed recently by an IARC Working Group (1985) which concluded that all the three principal types of lung cancer, *viz.* squamous cell, small cell and adenocarcinoma, were probably caused by smoking, although the relative risk was least extreme for adenocarcinoma. The results of the present study have therefore supported the IARC conclusion.

It should be noted, however, that the proportion of never-smokers was 62.4% in adenocarcinoma, as compared with 26.1% in squamous and small cell carcinoma; and that some of the adenocarcinomas among smokers may well not have been caused by smoking. The causes of the high rates of lung cancer, particularly adenocarcinoma in never smoking women in Hong Kong remained uncertain, and prompted the present study. Furthermore, this problem had become more urgent since Kung *et al.* (1984) showed that there appeared to have been an increase in the relative frequency of adenocarcinoma in both sexes in the comparison of their series of lung cancer cases in 1973–1982 with an earlier series in 1960–1972.

Since the publication of the results on passive smoking by Hirayama (1981) and Trichopoulos *et al.* (1981), passive smoking was postulated as a risk factor for lung cancer in never smoking women in Hong Kong and elsewhere. In Hong Kong, Chan and Fung (1982) reanalysed the case control study data of Chan *et al.* (1979) and found that among non-smoking women there were more passive smokers in controls (66/139) than cases (34/84). The 84 cases included 34 adenocarcinomas and other cell types. In a case control study by Koo *et al.* (1984) on 200 female lung cancer patients and 200 healthy district controls, 69 adenocarcinomas and 19 cases not confirmed pathologically were included. The RR in never smoked wives with smoking husbands was 1.48 ($P=0.16$) and is close to that in the present study (1.65). The RRs for passive smoking in never smoking females by cell types were: squamous cell 1.75, small cell 1.10, adenocarcinoma 1.11 and large cell 1.44 (Koo *et al.*, 1985). However, in a study by Lam (1985) on 163 female lung cancer cases and 185 orthopaedic controls, the author focussed the analysis for passive smoking on 60 adenocarcinoma cases and 144 controls, both cases and controls being non-smokers. For peripheral tumour, he found an increased RR of 2.64 ($P<0.05$) for passive smoking due to a smoking husband. For central tumours, the RR was 1.61, but was not significant. The RR for adenocarcinoma, central and peripheral tumour combined was 2.01 (95% CI = 1.09, 3.72; $P<0.05$; our calculation). Passive smoking in other cell types was not reported.

In the present study the overall RR for passive smoking due to a smoking husband was 1.65 ($P<0.01$) in all cell types combined. When broken down by cell types, a statistically significant RR was found only in adenocarcinoma but not in the other cell types, although this may have reflected chiefly the smallness of the numbers involved. The value of RR of 2.12 was very close to that of 2.01 reported by Lam (1985). The 95% CI for the present study (1.32, 3.39) was narrower than that in Lam's study (1.09, 3.72), however, because the number of subjects was smaller in the latter study. Analysis by central or peripheral positions of the tumour was not possible in the present study because of lack of information. It is probable that the true relative risk is nearer to the lower end (1.30) than to the upper end (3.36) of the confidence interval, because it is difficult to believe that passive exposure is more hazardous than active exposure, and for adenocarcinomas the relative risk (comparing all smokers with all never-smokers, including passively exposed never-smokers) for active smoking was only 1.87. The significant trends observed between RR and amount smoked daily by husband for all cell types combined and for adenocarcinoma provides support the view that the relationship is likely to be causal.

Recently, Blot and Fraumeni (1986) reviewed the epidemiological and other evidence on passive smoking and lung cancer and concluded that the existing evidence is highly suggestive that long-term exposure to environmental tobacco smoke increases the risk of lung cancer. Summarising the available data, they estimated that the excess risk was ~30%. The excess risk rose with increasing exposure, reaching ~70% among heavily exposed non-smokers. Wald *et al.* (1986) also calculated a relative risk of 1.35 for lung cancer among non-smokers living with smokers by pooling the results of 10 case control studies and three prospective studies and concluded that breathing other people's tobacco smoke is a cause of lung cancer. Compared to the 13 studies included by Wald *et al.* (1986) the present study included the largest series of never smoking lung cancer cases (199 cases). Results of the present study would add more evidence on passive smoking as a risk factor and they would contribute towards part of the explanation for the high incidence of lung cancer in never smoking women in Hong Kong.

With regard to the possibility of bias through the misclassification of current and ex-smokers as lifelong non-smokers, Wald *et al.* (1986) stated that the extent of misclassification bias was influenced by the proportions of men and women in the population who had smoked at some time and the greater the proportions (of women in particular), the greater the bias. By choosing the high proportions of 50% of smokers in women and 70% in men and a low observed relative risk of 1.35, they concluded that the misclassification bias was unlikely to account for all the association between lung cancer and passive smoking. In Hong Kong, the proportion of smokers in men was 32.8% and in women 4.1% (Hong Kong Census and Statistics Department, 1985). These figures, particularly in women, were much lower than the figures used by Wald *et al.* (1986). Also, the observed RR was higher in the present study. Thus the extent of influence by misclassification bias would be much less and could not account for the relatively high RR in the present study.

Furthermore, a comparison for adenocarcinoma on the RR due to active smoking (1.87) and that due to passive smoking (2.12) seemed to suggest that the risk for passive smoking was quite similar to that for active smoking for this particular cell type. This was not the case for all other cell types in which active smoking posed much higher risks than passive smoking. The apparently greater risk of adenocarcinoma than of other cell types from passive smoking conflicts with findings in other studies and this may be a feature of small numbers. However, Peto and Doll (1986) in their recent editorial on passive smoking stated that the observed risk need not necessarily be the same in all countries as type of tobacco, past changes in smoking habits, and the extent of passive exposure both at home and elsewhere may all differ substantially between different countries. In places like Hong Kong where people lived in more over-crowded conditions with poor ventilation, passive exposure may be heavier resulting in a higher RR. Moreover, Wynder and Goodman (1983) noted that the predominant cell type of lung cancer in non-smokers is adenocarcinoma and postulated that passive inhalation may primarily increase the risk for adenocarcinoma because side-stream smoke, which contains many gaseous components, can reach the deeper parts of the lung more readily than can mainstream smoke with more particulates. Together with the findings by Lam (1985) on peripheral adenocarcinoma, our results do offer some support for Wynder and Goodman's postulate that passive smoking may be a risk factor particularly for adenocarcinoma. At the very least, reviews

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Table IV Passive smoking due to a smoking husband (all forms of tobacco) in 199 never smoking cases and 335 never smoking controls by cell types

Cell type	Smoking history of husbands: Case No	Case Yes	Control No	Control Yes	Relative risk (& 95% CI)	P
Squamous cell carcinoma	15	12	37	35	0.85 (0.35, 2.06)	>0.05
Small cell carcinoma	2	6	18	18	3.00 (0.53, 16.90)	>0.05
Adenocarcinoma	53	78	92	64	2.12 (1.32, 3.39)	<0.01
Large cell carcinoma	2	7	8	9	3.11 (0.50, 19.54)	>0.05
Others and unclassified	12	12	28	26	1.08 (0.41, 2.82)	>0.05
All cell types	84	115	183	152	1.65 (1.16, 2.35)	<0.01

Notes: For each cell type, the cases were compared with their matched controls on passive smoking for ever smokers and never-smokers. Results on ever-smokers were not included here. One case and 2 controls with missing data on smoking and 3 cases and 2 controls with missing data on husband's smoking were excluded.

Table V Passive smoking due to a smoking husband (all forms of tobacco) in never smoking cases (all cell types and adenocarcinoma) and never smoking controls by amount of tobacco smoked daily by husband

Amount smoked daily by husband	All cell types: Case	Control	Relative risk (& 95% CI)	P	Adenocarcinoma: Case	Control	Relative risk (& 95% CI)	P
Nil	84	183	1		53	92	1	
1–10	22	22	2.18 (1.14, 4.15)	<0.05	17	12	2.46 (1.09, 5.54)	<0.05
11–20	56	66	1.85 (1.19, 2.87)	<0.01	37	28	2.29 (1.26, 4.16)	<0.01
21+	20	21	2.07 (1.07, 4.03)	<0.05	15	9	2.89 (1.18, 7.07)	<0.05
Total	182	292			122	141		
Test for trend	$\chi^2 = 10.17$, $P < 0.01$				$\chi^2 = 11.07$, $P < 0.001$			

Notes: Subjects with missing data on amount smoked daily by husband were excluded.

Discussion

The present study was a case control study on lung cancer in Hong Kong Chinese women with a larger number of subjects included than in the two previous local case control studies (Chan *et al.*, 1979; Koo *et al.*, 1984). All our cases were pathologically confirmed, unlike these two previous studies which included cases confirmed only by clinico-radiological criteria. The primary advantage of its relatively large-size (the largest such series yet reported) and the improvement over previous Hong Kong studies by including only pathologically confirmed cases enabled calculations of histologic-specific risk estimates.

The controls used were healthy women from the same neighbourhood matched for age. Comparability between cases and controls with regard to basic demographic variables was good, suggesting that these demographic variables may not have a major confounding effect on the results reported.

As shown in Table I, the distribution of cell type in the cases in the present study was comparable to the large pathological study of Kung *et al.* (1984) which included surgical material such as bronchial biopsy, trans-bronchial biopsy, needle biopsy and resection specimens. Biopsy of lymph nodes alone were not included. Cases without histological examination of the primary tumour of the lungs, or which were diagnosed by cytology alone were excluded. Despite the difference in the basis of diagnosis between the present study and that of Kung *et al.* (1984), the similarity in the results suggests that the cell type distribution observed in the present study should be close to the true distribution.

For smoking by the subject herself, the present study confirmed the increased risk of lung cancer found in previous studies in Hong Kong, but indicated a slightly higher relative risk (3.81) than in the study of Chan *et al.* (1979) (3.48) or of Koo *et al.* (1985) (2.77). The significant trend observed suggests that the association is likely to be causal.

With regard to cell types, statistically significant RRs were found for all cell types, including adenocarcinoma. In previous studies in Hong Kong, the RRs for adenocarcinoma were greater than unity but did not reach a statistically significant level, perhaps due to the smaller number of subjects studied (Chan *et al.*, 1979; Lam *et al.*, 1983; Koo *et al.*, 1985). This led to the hypothesis that smoking was not a risk factor for adenocarcinoma in Hong Kong Chinese women. The results of the present study suggest that smoking is significantly associated with adenocarcinoma, although to a lesser degree than with squamous or small cell carcinoma. The RR of 1.87 compared well with

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of passive smoking and lung cancer can no longer suggest that the results in Hong Kong fail to support the existence of a real relationship.

In conclusion, however, we note that 25.2% (53/210) of our patients with adenocarcinoma were neither smokers themselves nor passive smokers due to smoking husbands. Although smoking and passive smoking may account partly for the high incidence of adenocarcinoma, exposure to other factors should be further examined to elucidate the aetiology of lung cancer, particularly the high incidence of adenocarcinoma in this population.

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Pershagen, G., Hrubec, Z. and Svensson, C., "Passive Smoking and Lung Cancer in Swedish Women," American Journal of Epidemiology 125(1): 17-24, 1987.

Seventy-seven primary bronchial and lung cancer cases were identified by follow-up of a cohort of 27,409 nonsmoking Swedish women. All but one of the cases were histologically or cytologically confirmed. Two control groups of 184 women each, matched to cases for year of birth, were selected from the original cohort as well. Control Group 2 was matched on vital status as well. At least 90% of the questionnaires were answered by cases themselves. Questions concerned smoking by husband and by parents, although it is not clear from the paper whether the question about parents reflected childhood exposure.

For marriage to a smoker, and when both control groups were used, a RR of 3.3 (95% CI 1.1-11.4) was reported for squamous cell or small cell carcinoma. For all types of lung cancer, the RR reported was 1.2 (95% CI 0.7-2.1). The authors also claim that their data support a dose-response trend for squamous and small cell carcinoma with increasing smoking by husband. For all lung cancer cell types, a RR = 1.0 (95% CI 0.4-2.3) was reported for parental smoking.

The authors claim that their reported association between "passive smoking" and squamous and small cell lung cancers was not confounded by occupation, urbanization or living in houses with a greater risk of radon exposure.

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PASSIVE SMOKING AND LUNG CANCER IN SWEDISH WOMEN

GÖRAN PERSHAGEN,[1] ZDENEK HRUBEC,[1,2] AND CHRISTER SVENSSON[1]

Pershagen, G. (National Institute of Environmental Medicine, P.O. Box 60208, S-10401 Stockholm, Sweden), Z. Hrubec, and C. Svensson. Passive smoking and lung cancer in Swedish women. *Am J Epidemiol* 1987;125:17–24.

The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 nonsmoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a follow-up of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer which show the highest relative risks in smokers.

histology; lung neoplasms; smoking; tobacco smoke pollution

In recent years there has been a growing interest in the health effects of environmental tobacco smoke. Biologic monitoring has demonstrated that exposure to tobacco smoke constituents may be appreciable among passive smokers (1–4). Several studies show that children with parents who smoke have an increased risk of bronchitis and pneumonia, and some data also indicate changes of pulmonary function in adults and children exposed to environmental tobacco smoke (5).

A few epidemiologic studies have been published on passive smoking and lung cancer (6–17). Some of these show increased risks for nonsmokers married to smokers, but the results are not fully consistent. Most of the studies were not specifically designed to investigate effects of passive smoking, and there are various potential sources of random and systematic errors which make it difficult to interpret the findings. One aim of the present investigation was to try to minimize such errors, especially with regard to the validity of the information on exposure and effects.

MATERIALS AND METHODS

Study subjects

This investigation is designed as a case-control study within a cohort of nonsmoking women. There are two sources for the cohort. Most of the subjects are taken from a sample of about 55,000 men and women aged 15–65 years in the 1960 National Census of Sweden for whom tobacco smoking was investigated by a questionnaire mailed in 1963. Detailed descriptions of the sampling strategy and the questionnaire are

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[1] Department of Epidemiology, National Institute of Environmental Medicine, P.O. Box 60208, S-10401 Stockholm, Sweden. (Reprint requests to Dr. Göran Pershagen.)

[2] Present address: Radiation Epidemiology Branch, National Cancer Institute, Bethesda, MD.

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given elsewhere (18). The response rate among the women was 95.4 per cent. A total of 17,679 (66.8 per cent) of the women stated that they had never smoked any form of tobacco, and these are included in the present study.

The second source of subjects is the "old" Swedish twin register which contains about 11,000 same-sex twin pairs born between 1886 and 1925 (19). The twins were identified from birth certificates, and a questionnaire was mailed to them in 1961, primarily to determine zygosity and tobacco smoking status. The response rate among the eligible female twin pairs was 85.1 per cent. In all, 9,730 women (80.6 per cent) had never smoked, and they make up the rest of the study cohort.

Cancer morbidity and mortality of the 27,409 women in the study cohort were determined through 1980 in the Swedish Cancer Register and the National Register on Causes of Death, respectively. The quality of the information in these registers is high for most cancer diagnoses (20). A total of 92 cases of tracheal, bronchial, lung, or pleural cancer were identified (*International Classification of Diseases* (ICD), Seventh Revision, codes 162–163) (21). These subjects constitute the case series.

Two control groups, each containing two controls per case, were also selected from the study cohort. Control group 1 consisted of subjects who were matched to their respective case on year of birth (±1 year). Control group 2 included subjects who were matched on year of birth as well as on vital status at end of follow-up. The subjects in both control groups were selected at random from subjects who fulfilled the matching criteria, with the exception that no woman could be used as a control for her twin sister. The entire study group consisted of 460 subjects: 58 cases and 232 controls from the 1963 smoking sample, as well as 34 cases and 136 controls from the twin register.

Exposure information

There were two sources of exposure information. First, as described above, data in the 1961 and 1963 questionnaires were used to define the cohort from which the cases and controls originated. The second source was a questionnaire mailed in 1984 to each study subject or, if she was dead, to the next-of-kin (excluding the husband), in order to validate the data on smoking as well as to assess the exposure to environmental tobacco smoke from husbands and parents. If a woman had been married more than once, smoking was investigated only for the man with whom she had cohabited the longest. Questions on occupational and residential history were also included. If the questionnaire answers were incomplete, additional information was obtained by telephone interview. The methodology using next-of-kin to obtain data has been shown to provide exposure information of high quality (22–24).

The residential history information from the 1984 questionnaire included data on addresses (parishes) and types of houses in which the study subjects had lived. A parish was classified as urban if 90 per cent or more of the population lived in built-up areas according to the 1970 National Census. One-family houses made of material other than wood and with basements were classified as dwellings presenting a greater risk of radon exposure. Indoor radon measurements show that the average concentrations in such houses are higher than in other common types of dwellings in Sweden (25).

Statistical methods

Several methods have been used in the statistical analysis. The matching was retained in some analyses, and maximum likelihood estimates of relative risks (approximated with odds ratios) and exact confidence intervals were computed according to the method of Miettinen (26). In other analyses, the matching was dissolved, and the relative risks and confidence intervals were estimated as suggested by Mantel and Haenszel (27) and Cornfield (28), respectively. The method proposed by Mantel (29) was used to test linear trends in these analyses. Besides the conventional strati-

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fied analyses, a conditional logistic regression analysis (30) was carried out in an attempt to control residual confounding in the risk estimates and to study interactions.

RESULTS

A careful review of the medical records of the 92 lung cancer cases showed that in nine cases the primary site was not the bronchus or lung (there were no primary tracheal or pleural carcinomas), and in six cases the primary site was uncertain. Carcinoma of the breast, which occurred in five cases, was the most common cause of secondary carcinomas. For 64 of the 77 primary carcinomas of the bronchus or lung, the diagnoses were based on histologic evidence, and for 12 diagnosis was based on cytology. In one case, an autopsy was performed, but there was no histologic examination.

The distribution of histologic types among the primary bronchial and lung carcinomas is shown in table 1. The classification is based on the information in the medical records, particularly the pathology reports. Adenocarcinoma is the most common group, constituting 57.1 per cent of the total. Squamous cell and small cell carcinomas constitute 31.2 per cent. The average ages at diagnosis and at death for the whole group of carcinomas are 69.0 and 69.6 years, respectively. In the following analysis, the squamous cell and small cell carcinomas are grouped together because these types have generally shown the highest relative risks among smokers (31).

TABLE 1

Histopathology of primary bronchial and lung carcinomas and mean ages at diagnosis and at death in a cohort of 27,409 nonsmoking Swedish women

Diagnosis	No.	%	Age (years)	
			Diagnosis	Death
Squamous cell carcinoma	12	15.6	68.5	70.1
Small cell carcinoma	12	15.6	65.6	65.8
Adenocarcinoma	44	57.1	69.7	70.2
Large cell carcinoma	5	6.5	67.9	68.0
Other primary carcinomas	4	5.2	74.4	74.8
Total	77	100.0	69.0	69.6

Table 2 shows the distribution of selected variables among the cases and the control groups. As a result of the matching criteria, the age distribution and vital status are similar for the cases and control group 2. In control group 1, there is a shift toward older ages, and more subjects were alive at the end of follow-up than in the two other groups.

Questionnaires were returned for 90.2–96.7 per cent of the study subjects in the different groups. Among the proxy respondents, 68.4 per cent were children of the study subjects, 21.3 per cent were brothers or sisters, and 10.3 per cent were other relatives. There were no differences in the type of proxy respondents between the case and control groups.

All of the returned questionnaires contained information on smoking by the study subject and, with the exception of one subject in each control group, on whether she had been married and whether her husband had smoked. For the other questionnaire items, e.g., smoking habits of parents, employment, and residential history, the internal nonresponse rates ranged from 9.6–32.6 per cent. The percentages in table 2 are based on the number of respondents to each item.

Eight (1.8 per cent) of the 436 women for whom questionnaire information could be obtained in 1984 had smoked daily during at least two years. Four of these had stopped before answering the 1961 or the 1963 questionnaire, and one had started after that. Two women smoked 1–7 cigarettes per day, and one was a pipe smoker. These eight women were excluded in the subsequent analyses. There were no pronounced differences between the groups with regard to the percentage of women who were married or the percentage who were married to smokers.

For the remainder of the questionnaire items, no consistent differences were seen between the groups, with the possible exception of a tendency toward a larger per-

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TABLE 2

Distribution of selected variables among cases of lung cancer and two control groups matched for year of birth, from a cohort of nonsmoking women

	No.			%		
	Cases	Control group 1	Control group 2	Cases	Control group 1	Control group 2
Total	92	184	184	100	100	100
Localization of primary tumor						
Bronchus or lung	77			83.7		
Other site or uncertain	15			16.3		
Age at death or at end of follow-up (years)						
40–69	44	38	93	47.8	20.7	50.5
70–79	40	90	73	43.5	48.9	39.7
80–91	8	56	18	8.7	30.4	9.8
Vital status at end of follow-up						
Alive	5	121	10	5.4	65.8	5.4
Dead	87	63	174	94.6	34.2	94.6
Total questionnaire respondents	83	178	175	90.2	96.7	95.1
Smoked daily†	2	3	3	(2.4)*	(1.7)	(1.7)
Married†	70	143	151	(84.3)	(80.3)	(86.8)
Married to smoker†	37	76	77	(44.6)	(42.9)	(44.3)
At least one parent smoker†	12	30	21	(21.1)	(21.4)	(15.9)
Employed outside home†	33	73	52	(44.0)	(48.3)	(34.7)
Lived in urban area†	39	78	82	(60.9)	(61.4)‡	(62.6)
Lived in dwelling presenting a greater risk of radon exposure†	11	13	9	(17.2)	(10.8)‡	(7.0)

* Numbers in parentheses correspond to percentages of total number of questionnaire respondents to each item.

† Minimum duration of two years.

‡ Exposures occurring after the death of their respective case have been excluded for controls alive at the end of follow-up.

centage of cases than of controls who lived in dwellings presenting a greater risk of radon exposure. A detailed analysis of the occupations held by the cases and controls did not reveal any differences between the groups. The great majority of the occupations were in the service sector and typical for women of the age group under study, e.g., housemaid, cook, seamstress, cleaner, and nurse.

In the following analyses, the 15 cases with primary sites other than the bronchus or lung have been excluded. Table 3 gives, in a matched analysis, the relative risks for primary carcinoma of the bronchus or lung in women married to smokers. Never married women and women married to nonsmokers constitute the reference category. The results are consistent for both control groups. Pooling the control groups produces a relative risk of 3.3 for squamous cell and small cell carcinomas (95 per cent confidence interval (CI) = 1.1–11.4) associated with marriage to a smoker. Within this group, the relative risks were increased for both histologic types. The relative risks for the other histologic types and for the entire group are 0.8 (95 per cent CI = 0.4–1.5) and 1.2 (95 per cent CI = 0.7–2.1), respectively.

Table 4 gives a dose-response analysis with regard to smoking by the husband. The matching was dissolved in this analysis as well as in table 5. There is a positive trend in the relative risk for squamous cell and small cell carcinomas ($\chi^2 = 3.9$), but not for the other histologic types. The relative risk in the highest exposure group, i.e., women with husbands who smoked more than 15 cigarettes per day or one pack

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TABLE 3

*Relative risks (RR) and 95% confidence intervals (CI) for primary carcinoma of the bronchus or lung in nonsmoking women married to smokers with two control groups in a matched analysis**

Histologic type	No. of cases	Control group 1†		Control group 2‡		Both control groups	
		RR	CI	RR	CI	RR	CI
Squamous cell or small cell carcinoma	20	3.8	1.1–16.9	3.4	0.8–20.1	3.3	1.1–11.4
Other types	47	0.7	0.3–1.6	0.8	0.4–1.7	0.8	0.4–1.5
Total	67	1.2	0.6–2.2	1.1	0.6–2.1	1.2	0.7–2.1

* Never married women and women married to nonsmokers constitute reference category. Maximum likelihood estimates of relative risks and exact confidence intervals (26).

† Matched to cases on year of birth.

‡ Matched to cases on year of birth as well as on vital status at end of follow-up.

TABLE 4

*Relative risks (RR) and 95% confidence intervals (CI) for primary carcinoma of the bronchus or lung in nonsmoking women in relation to estimated exposure to tobacco smoke from the husband**

Histologic type	Never married or married to a nonsmoker		Low exposure to tobacco smoke of husband†			High exposure to tobacco smoke of husband‡			Chi-square for trend§
	No. of cases	RR	No. of cases	RR	CI	No. of cases	RR	CI	
Squamous cell or small cell carcinoma	7	1.0	10	1.8	0.6–5.3	3	6.4	1.1–34.7	3.90
Other types	27	1.0	16	0.8	0.4–1.6	4	2.4	0.6–8.7	0.03
Total	34	1.0	26	1.0	0.6–1.8	7	3.2	1.0–9.5	1.45

* Age-standardized relative risk estimates (27) and approximate confidence intervals (28).

† Husband smoking up to 15 cigarettes per day or one pack (50 g) of pipe tobacco per week or any amount during less than 30 years of marriage.

‡ Husband smoking more than 15 cigarettes per day or one pack of pipe tobacco per week during 30 years of marriage or more.

§ Test for linear trend (29).

of pipe tobacco per week during 30 years of marriage or more, is 3.2 (95 per cent CI = 1.0–9.5) for all histologic types combined.

Table 5 shows the influence of parental smoking on the risk of primary carcinoma of the bronchus or lung, controlling for smoking by the husband. There is no consistent evidence of an effect, and the 95 per cent confidence intervals for the relative risks in women with at least one smoking parent encompass 1.0 for both histologic groups. These results must be interpreted with caution in view of the lack of information on parental smoking habits for 24 per cent of the questionnaire respondents.

The results of the conditional logistic regression analysis, which included cases and matched controls with information on all variables, were consistent with the results of the stratified analyses. There was no important confounding of the association between smoking by the husband and squamous cell and small cell carcinomas by occupation, by living in houses with a greater risk of radon exposure, or by living in urban areas. None of the relative risks associated with these factors deviated significantly from 1.0 upon statistical testing. For all histologic types taken together, the relative risks and 95 per cent confidence intervals associated with marriage to a smoker and with living in a house presenting a greater risk of radon exposure were 1.2 (95 per cent CI = 0.6–2.6) and 1.4 (95

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TABLE 5

*Relative risks (RR) and 95% confidence intervals (CI) for primary carcinoma of the bronchus or lung in nonsmoking women in relation to smoking habits of parents**

Histologic type	Both parents nonsmokers		At least one smoking parent		
	No. of cases	RR	No. of cases	RR	CI
Squamous cell or small cell carcinoma	10	1.0	6	1.9	0.5–6.2
Other types	28	1.0	3	0.5	0.1–1.9
Total	38	1.0	9	1.0	0.4–2.3

* Mantel-Haenszel estimates of relative risks (27) standardized for age and smoking of husband with approximate confidence intervals (28).

per cent CI = 0.4–5.4), respectively. For women who had been married to a smoker and who had lived in a house presenting a greater risk of radon exposure the relative risk was 2.5 (95 per cent CI = 0.8–8.5), suggesting a positive interaction between the two variables.

DISCUSSION

The results of our study indicate that exposure to environmental tobacco smoke is related to an increased risk of those histologic types of lung cancer which show the highest relative risks in smokers. This is in general agreement with the findings of Trichopoulos et al. (7), Garfinkel et al. (15), and Koo et al. (16), although these authors looked at somewhat different carcinoma types and/or used other definitions of exposure. It would be of interest to see an analysis of the risks for different histologic types in the other published studies on passive smoking and lung cancer, especially those with an appreciable number of cases, as well as in subsequent studies on this topic.

Combining the published epidemiologic studies provides a weighted average relative risk of lung cancer of 1.5 associated with marriage to a smoker (5). The results of the present study are consistent with this estimate. A 50 per cent increase in risk does not seem unreasonable in view of exposure estimates among passive smokers (5, 32) and the excess risks of between 100 and 900 per cent for smokers in the lowest exposure category, as a rule 1–9 cigarettes per day, in the major cohorts studied (18, 33–39). It should be noted that relative risks for squamous cell and small cell carcinomas would be expected to be even higher, i.e., if the case group is not "diluted" with adenocarcinomas or other types with weaker association to smoking.

Several sources of random and systematic errors have to be considered in the interpretation of the findings. In contrast to earlier studies on passive smoking and lung cancer, the present study has a "double check" on the smoking status of all study subjects. Data were obtained from the 1961 and 1963 questionnaires that were used to define the cohort as well as from the 1984 questionnaire. Our results indicate that misclassification of nonsmokers was a minor problem and that failure to take this problem into account would not severely bias the association between passive smoking and lung cancer. This is supported by the findings of other Swedish studies, which show a high quality of questionnaire information on smoking, both when the data were obtained from the subjects themselves and when data were obtained from next-of-kin (22, 23).

Using smoking by the husband as the only measure of exposure to environmental tobacco smoke will result in misclassifications in the exposure assessment. To the extent that such misclassifications are unrelated to the disease in question, this would tend to reduce any true association between passive smoking and lung cancer. The similar percentages of exposed persons among the cases, excluding squamous cell and small cell carcinomas, and the two control groups suggest that errors in the reporting did not affect the cases and controls differently. This lends further support to the association with smoking of the husbands, which was noted for squamous cell and small cell carcinomas only. Obviously,

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it is unlikely that the next-of-kin respondents were aware of the histologic subtypes diagnosed for the cases.

Our results show that poor quality of the diagnosis may be a problem in studies of lung cancer in female nonsmokers. Secondary pulmonary carcinomas or carcinomas with unknown primary sites appeared in about one-sixth of the cases reported in the cancer and/or cause of death registers. This is in close agreement with the findings of Garfinkel (8), which were based on death certificate diagnoses in the United States. If secondary tumors are not excluded from the case series, the relative risks associated with any factor that causes primarily lung carcinomas are likely to be underestimated. As noted previously, the analysis may be further strengthened by separating different histologic types.

Besides the quality of the exposure and diagnostic information, the validity of our study is also affected by the control of confounding factors. The association between passive smoking and lung cancer of the squamous cell and small cell types was not confounded by occupation, urbanization, or living in houses with a greater risk of radon exposure nor were any of these factors associated with a clear increase in risk when passive smoking was controlled. These findings should be interpreted with some caution in view of the internal nonresponse on the questionnaire for items other than smoking of the study subjects and their spouses. It is, however, improbable that uncontrolled confounding by the factors under study explains relative risks of the magnitude observed, as well as the positive dose-response relations. No information was obtained on intake of food items that may affect the lung cancer risk.

Analysis of all the lung cancer cases suggested a positive interaction between marriage to a smoker and living in dwellings presenting a greater risk of radon exposure, i.e., one-family houses made of material other than wood and with a basement. Increased risks of lung cancer associated with living in such houses have been observed previously (40–42), but our study also provides data on exposure to environmental tobacco smoke. Our findings are consistent with an interaction between tobacco smoke and radon daughters similar to the one observed in uranium miners (43) and in smokers living in dwellings with a greater risk of radon exposure (41). It is also of interest to note that the radon daughter concentration has been shown to increase considerably as a result of attachment to aerosol particles in rooms filled with tobacco smoke (44).

In conclusion, our results indicate that exposure to environmental tobacco smoke is related primarily to those forms of lung cancer which show the highest relative risks in smokers. The results are internally consistent and in general agreement with other studies. Our findings are of scientific interest and have public health implications, although it is obvious that lung cancer in passive smokers is a rare phenomenon. The accumulating evidence in children and adults shows that serious health effects can probably result from heavy exposure to environmental tobacco smoke. This should encourage further research, including both exposure assessments and etiologic studies.

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Geng, G.-Y., Liang, Z.H., Zhang, A.Y. and Wu, G.L., "On the Relationship Between Smoking and Female Lung Cancer," Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 483-486.

Women in Tianjin, China were investigated in this case-control study (157 cases, 157 controls, matched for age, sex, race and marital status). Histological confirmation was available for 85% of cases. The authors reported elevated ORs associated with active smoking. ETS exposure was estimated using questions about smoking of husband, father, mother and colleagues.

The authors reported an OR of 2.16 (95% CI 1.03-4.53) for husband's smoking; analyses based on the other estimates of exposure were not given, although the authors stated that they were not significant. The authors also reported that ORs for lung cancer in women increased with either the number of cigarettes smoked per day by the husband or with years of exposure to husband's smoking. Statistical analyses of the "trends" were not presented.

Elevated ORs for history of lung disease (2.12, 95% CI 1.23-3.63) and for cooking with coal (from 1.54 to 5.56, for various indices of exposure) were also reported, as was increased risk associated with some occupational exposures (textile workers, workers exposed to asbestos, workers exposed to benzene, OR = 3.1, 95% CI 1.58-6.02).

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Editors:

Masakazu Aoki
Tuberculosis Institute, Kiyose, Tokyo, Japan

Shigeru Hisamichi
Tohoku University School of Medicine, Sendai, Japan

Saketami Tominaga
Aichi Cancer Center Research Institute, Nagoya, Japan

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Smoking and health 1987 M. Aoki et al. editors

ON THE RELATIONSHIP BETWEEN SMOKING AND FEMALE LUNG CANCER

YUAN-YI PENG, Z.H.LIANG, A.Y.ZHANG, Z.L.WU
Department of Epidemiology, Tianjin Medical College, Tianjin (P.R.China)

There is still controversy about the relationship between cigarette smoking and female lung cancer. The mortality rate of female lung cancer in Tianjin is the highest in China ($28.3/10^5$). The female smoking rate in Tianjin is also the highest in China. Therefore we had conducted a case-control study of female lung cancer to illustrate it.

MATERIAL AND METHODS

We conducted a 1:1 pair matched case-control study.

1. Cases: 157 female lung cancer cases all resident in Tianjin more than 10 years. Squamous cell carcinoma 35(22.3%); Small cell carcinoma 31(19.7%); Adenocarcinoma 58(36.9%); Large cell carcinoma 4(2.5%); Cell type unknown 29(18.5%). Cases were diagnosed: 133(84.7%) histologically or cytologically; 17(10.8%) by CT; 7(4.5%) clinically or by X-ray.

2. Controls: 157, matched with sex, race, age(±2 years) and marital status.

RESULTS

1. The case group is a quite representative of the Tianjin female lung cancer. The age group structure and distribution of residents of the lung cancer group is quite similar with those of 1983 Tianjin female lung cancer. Smoking rate of the control group(40.8%) is quite similar with that of the Tianjin adult female population(39.5% &58%).

2. The age, education, occupation, race, marital status, birth place, resident place of the case and control groups have no significant difference($P>0.05$).

3. Female lung cancer and active smoking

~~are: Active smoking is 3.05, PAR% is 57.4%~~ (Table 1).

TABLE 1. OR OF SMOKING

		Controls	
		Smoker	Nonsmoker
Cases	Smoker	45	58
	Non-smoker	19	35

OR=3.05, 95%CI=1.77-5.30
Adjusted OR=2.6, 95% CI=1.4-4.6, $P<0.001$

Exposure rate of cases:

$$\frac{45+58}{157}=65.6\%$$

$$PAR\%=\frac{.656(3.05-1)}{.656(3.05-1)+1}=57.4\%$$

~~There is quite obvious dose-effect relationship between lung cancer risk and number of cigarettes smoked per day and year of smoking~~ (Table 2).

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OR is higher of those smoking deeper than those smoke superficially or non-smoking (Table 3). OR is higher among those start smoking earlier (Table 4).

TABLE 2. LUNG CANCER RISK AND NO. OF CIGARETTES AND YEAR OF SMOKING

No. of cigarettes/day	OR	95% CI of OR
0-	1	
1-	1.81	1.40-2.33
11-	3.27	2.28-4.68
21-	5.90	3.79-9.18
Year of smoking		
0	1	
1-	1.73	1.38-2.18
20-	3.00	2.17-4.16
40-	5.20	3.49-7.75

TABLE 3. OR AND DEGREE OF INHALATION (M-H METHOD)

	No	Occasional	Deep
Case	54	37	66
Control	98	33	26
OR	1	2.03	4.61

P<0.01

TABLE 4. OR AND AGE ONSET OF SMOKING (M-H METHOD)

Age	Group	Non-smoking	21	16-20	15	P
<44	Case	8	1	3	0	>0.05
	Control	12	0	1	0	
45-	Case	16	8	17	14	<0.01
	Control	29	9	14	3	
55-	Case	24	13	13	15	<0.01
	Control	35	18	6	5	
65-	Case	6	6	6	7	<0.01
	Control	17	4	2	2	
	OR	1	1.59	3.10	6.3	<0.01

4. Female lung cancer and passive smoking.

We had calculated the OR of passive smoking from husband, father, mother and colleagues, only that from husband is quite significant.

The non-smoking female cases and controls with smoking or non-smoking husband is as table 5. The OR is 2.16 (P<0.05).

TABLE 5. OR OF SMOKING HUSBAND TO NON-SMOKING WIFE

	Husband	
	Smoker	Non-smoker
Case	34	20
Control	41	52

OR=2.16, 95% CI=1.03-4.53,
P<0.05

Exposure rate of cases

$$= \frac{34}{34+20} = 0.63$$

$$PAR = \frac{.63(2.16-1)}{.63(2.16-1)+1} = 42.2\%$$

OR of female lung cancer increases with the number of cigarettes smoked per day by her hus-

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and the duration of exposure to her husband's smoking(Table 6).

5.OR of either active or passive and combination of active and passive smoking is as table 7.

TABLE 6.OR OF FEMALE LUNG CANCER OF SMOKING HUSBAND

HUSBAND SMOKING	OR	95%CI OF OR
CIGARETTE PER DAY		
0	1	
1-	1.40	1.12-1.76
10-	1.97	1.42-2.72
20-	2.76	1.85-4.10
YEARS OF SMOKING		
0	1	
1-	1.49	1.15-1.94
20-	2.23	1.54-3.22
40-	3.32	2.11-5.22

TABLE 7.OR OF ACTIVE AND PASSIVE SMOKING FROM HUSBAND

		ACTIVE SMOKING(WIVES)	
		NO	YES
HUSBAND SMOKING	NO	1.0	2.61(1.4-4.6)
	YES	1.86(1.04-3.5)	4.90(1.8-9.5)

If a smoking woman with smoking husband,the OR of lung cancer is 4.9,exposure rate is 81% (83/103).

$$PAR\% = \frac{.81\ (4.9 - 1)}{.81(4.9-1) + 1} = 75.95\%.$$

A non-smoking woman with smoking husband,the OR of lung cancer is 1.86,exposure rate is 63% (34/54).

$$PAR\% = \frac{.63\ (1.86 - 1)}{.63(1.86-1) + 1} = 35.1\%.$$

According to 103 smoking female lung cancer cases about 78.23(103 X .7595) are due to smoking,while the 54 non-smoking female lung cancer cases about 18.95(54 X .351) are due to passive smoking from her husband.

That is $\frac{78.23+18.95}{103+54} = 61.9\%$ of female lung cancer in Tianjin may attribute to active smoking and passive smoking from their husbands.

6. OR of female lung cancer due to other causes.

Occupational exposure: Textile workers,workers expose to asbestos, benzene,etc. CR=3.1,95% CI=1.58-6.02.

OR of history of lung diseases (include pulmonary TBC,chronic bronchitis,pulmonary infection,etc.)is 2.64.Adjusted with conditional regression model,OR=2.12,95%CI of OR=1.23-3.63.

OR of lung cancer and cooking with coal is shown in table 8.

7. Joint Effect of the Risk Factors.

Multifactor analysis by conditional regression method demonstrate that the combination of active smoking,passive smoking from husbands, occupational exposure,history of lung diseases and 4×10^4 hours cooking with coal makes the OR being about 50 in comparison with those

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without the above risk factors and cooking with coal less than $3X10^4$ hours. 95% CI of OR=13.7-185.3.

TABLE 8. OR OF LUNG CANCER AND COOKING WITH COAL

DURATION OF COOKING(hrs)	OR	95% CI of OR
$1x10^4$(1.5 hr/day,20 yrs)	1.54	1.20-1.96
$2x10^4$(1.5 hr/day,40 yrs)	2.36	1.66-3.34
$3x10^4$(2 hrs/day,42 yrs)	3.62	2.36-5.55
$4X10^4$(3 hrs/day,37 yrs)	5.56	3.40-9.10

CONCLUSION

1. Both active smoking and passive smoking from her husband are the most important risk factors of female lung cancer in Tianjin. About 60% of female lung cancer in Tianjin may be attributed to smoking.

2. There is joint effect of smoking with occupational exposure,history of lung diseases and cooking with coal.

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Inoue, R. and Hirayama, T., "Passive Smoking and Lung Cancer in Women" Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 283-285.

This case-control study was conducted in two Japanese cities: Kamakura, a "residential community" and Miura, a city characterized by "fishery industry." Only 29 female cases and 54 controls were included. Elevated RRs for personal smoking were reported.

In an analysis controlling for city and age, RRs of lung cancer for nonsmoking women of 2.58 (95% CI 0.44-5.70) when husbands smoked less than 19 cigarettes/day and 3.09 (95% CI 1.04-11.81) when husbands smoked 20 or more cigarettes per day were reported. The authors claimed that these two estimates supported a trend of increasing risk with increasing exposure.

No potential confounders other than city were included.

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PASSIVE SMOKING AND LUNG CANCER IN WOMEN

REIKO INOUE, TAKESHI HIRAYAMA*

Kanagawa Cancer Center, Asahi-ku, Yokohama 241, Japan
Institute of Preventive Oncology, Shinjuku-ku, Tokyou 162, Japan*

INTRODUCTION

A case-control study on smoking and lung cancer was conducted in two cities in Kanagawa prefecture Japan distinctly different in social environment (Kamakura and Miura, featured by residential community and fishery industry respectively). A significant dose-responce relationship was observed between the number of cigarettes smoked daily and the risk of lung cancer. The risk of lung cancer was significantly higher, the earlier the age at start of smoking.These results clearly explain the reason of the rapid increase in lung cancer mortality in recent years in men. The increase in lung cancer mortality in women, however, is difficult to be explained by the influence of active smoking only, because the majority of lung cancer patients are non-smokers in case of women. Therefore passive smoking has come to be suspected as the possible causative factor of lung cancer in women. Epidemiological studies thus for reported since 1981 mostly suggest such possibility (1-7). Therefore the role of passive smoking on lung cancer in women was examined in the present case-control study.

MATERIALS AND METHODS

Husbands smoking habit of 37 cases of women died of lung cancer in Kamakura and Miura (13 cases in Kamakura, 1980-1983 and 24 cases in Miura, 1973-1981) were compared with 74 cases died of cerebrovascular disease during the same period. The cases and the controls were matched to age (year of birth), year of death (± 2.5 years) and the district. Cerebrovascular disease cases were selected as controls because the disease is known to be related neither to active nor to passive smoking. Interviews were conducted by trained local public health nurses and midwives using standard questionnaires. Mantel-Haenszel odds ratio was calculated for relative risk (r.r.) with 90% confidential intervals.

RESULTS

Active smoking (direct smoking)

24.3% of women smoked in case group (smokers 9, non-smokers 28), and 16.2% smoked in control group (smokers 12, non-smokers 62), relative risk (r.r.)(M.H.odds ratio) being 1.66 (0.73-3.76).

Passive smoking (indirect smoking)

The husbands smoking status was available for 29 cases out of 37 cases and for

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54 cases out of 74 controls. Before conducting the analysis a survey was made for 133 smoking men to study how many cigarettes were smoked daily at home. The result showed that none of the smokers of less than four cigarettes a day smoked at home. Since the purpose of our study is to examine the effects of passive smoking at home, the smokers kho smoked at least five cigarettes a day were considered as "smokers at home" in the present study.

When the lung cancer risk for non-smoking women was observed according to the smoking habit of their husbands. The relative risk (r.r.)(M.H.odds ratio) was 2.25 (0.91-7.10) for non-smoking wives with smoking husbands compared to non-smoking wives with non-smoking husband. Observation by number of cigarettes smoked per day revealed that r.r. for "less than 19 cigarettes" was 1.16 (0.28-4.84)($P > 0.05$) (cases 3, cont. 11), and for "more than 20 cigarettes" 3.35 (1.17-9.67)($P = 0.051$)(cases 15, cont. 19),(chi-square value for trend 4.06 $P < 0.05$). The relative risk of lung cancer in women who themselves smoke was 4.25 (1.22-14.83) ($P = 0.059$)(cases7, cont.7). (chi-square value for trend 5.46) ($P<0.05$).

When stratified by age groups the relative risk was 1.39 (0.29-4.91) in non-smoking women with husbands smoking "less than 19 cigarettes a day". It was 3.16 (1.06-9.60) when husbands smoked "more than 20 cigarettes a day", chi-square value for trend being 3.90 ($P < 0.05$). r.r. (M.H.odds ratio) for "smoking women" was 4.73 (1.22-15.35)($P < 0.05$). The chi-square value for trend including smoking women was 5.48 ($P<0.05$).

When both age groups and districts were stratified, r.r. (M.H.odds ratio) was 2.58 (0.44-5.70) when husbands smoked "less than 19 cigarettes" and 3.09 (1.04-11.81) when husbands smoked "20 or more cigarettes daily". The chi-square value for trend was 4.25 ($P<0.05$). The relative risk for smoking women was 5.50 (1.06-17.30). The chi-square value for trend including smoking women was 5.17 ($P<0.05$).

DISCUSSION

A case-control study on passive smoking and lung cancer in women was conducted in two cities distinctly different with regard to social environment. When both districts (social environment) and age group were stratified, relative risk of lung cancer in non-smoking wives was shown to be 2.58 when husbands smoked "less than 19 cigarettes a day" and 3.09 when husbands smoked "20 or more cigarettes a day". The relative risk of active smoking (direct smoking) was 5.50 which was higher than the effect of passive smoking. Although study size is quite small,the present study might to considered to provide an another evidence favoring the passive smoking and lung cancer hypothesis. Smoking at home shuld therefore be restricted strictly in oder to prevent non-smoking family members from suffering unnecessarily from lung cancer and other selected diseases.

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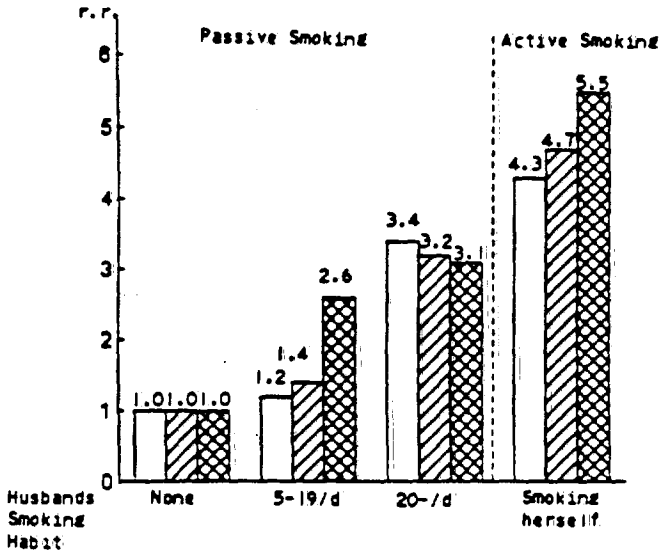

Chi-square for trend

	passive smoking	including active smoking
crude	4.06	5.46
age stratified	3.90	5.48
age-district stratified	4.20	5.17

Fig. Relative Risk for Lung Cancer in Non-smoking Wives by Husbands Smoking Habit
(A case-control study, Kamakura and Miura, Kanagawa prefecture, Japan)

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Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.

This case-control study of women in Nagoya, Japan (90 nonsmoking cases and 90 age-and hospital-matched controls) was conducted to investigate the significance of "passive smoking" and other factors in relation to lung cancer etiology.

Elevated RRs were reported for smoking by case's mother or husband's father living with the case (RR = 4.0, $p < 0.05$ and RR = 3.2, $p < 0.05$, respectively) [CIs were not given]. No association was reported for lung cancer risk and husband's smoking (RR = 1.1) or for ETS exposure at work (RR = 1.2).

A RR of 4.8 ($p < 0.05$) was reported for occupational exposure to iron or other metals; an elevated, statistically nonsignificant RR of 3.3 was reported for occupational exposure to coal, stone, cement, asbestos, or ceramics. The authors stated that no appreciable differences in food intake were observed between cases and controls, although the assessment of dietary differences was not detailed. The authors also present calculations for statistically nonsignificant elevated risks associated with the use of kerosene (RR = 1.6) and coal (RR = 1.7) in the household heating system. An elevated RR of 2.0, which was not statistically significant, was reported for personal history of silicosis.

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Tohoku J. exp. Med., 1988, 154, 389-397

A Case-Control Study of Lung Cancer in Nonsmoking Women

HIROYUKI SHIMIZU, MUNEHIKO MORISHITA,* KATSUYUKI MIZUNO,† TAKAO MASUDA,‡ YUKIO OGURA,‡ MITSUHIKO SANTO,‡ MINORU NISHIMURA,§ KAZUO KUNISHIMA,‖ KAZUO KARASAWA,‖ KEISUKE NISHIWAKI,¶ MASAHIKO YAMAMOTO,* SHIGERU HISAMICHI and SUKETAMI TOMINAGA**

*Department of Public Health, Tohoku University School of Medicine, Sendai 980, *the Second Department of Internal Medicine, Nagoya City University, Medical School, Nagoya 467, †the Third Department of Internal Medicine, Aichi Medical University, Aichi 480-11, ‡Department of Internal Medicine, National Nagoya Hospital, Nagoya 460, §Department of Internal Medicine, Aichi Cancer Center Hospital, Nagoya 464, ‖Department of Surgery, Aichi Cancer Center Hospital, Nagoya 464, ¶Department of Internal Medicine, Chukyo Hospital, Nagoya 457 and **Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya 464*

SHIMIZU, H., MORISHITA, M., MIZUNO, K., MASUDA, T., OGURA, Y., SANTO, M., NISHIMURA, M., KUNISHIMA, K., KARASAWA, K., NISHIWAKI, K., YAMAMOTO, M., HISAMICHI, S. and TOMINAGA, S.: *A Case-Control Study of Lung Cancer in Nonsmoking Women*. Tohoku J. exp. Med., 1988, 154 (4), 389-397 —— A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated relative risk (RR) of lung cancer was observed for passive smoking from mother (RR = 4.0; $p < 0.05$) and from husband's father (RR = 3.2; $p < 0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR = 4.8; $p < 0.05$). No appreciable differences in food intakes were observed between cases and controls. ———— lung cancer; women; nonsmoker; passive smoking; metal exposure

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Reprint requests: Dr. Hiroyuki Shimizu, Department of Public Health, Tohoku University School of Medicine, 2-1 Seiryo-machi, Sendai 980, Japan.

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The causes of lung cancer in Japanese women have not been clearly identified. It is widely accepted that cigarette smoking is causally associated with lung cancer, but the increasing trend in the incidence of lung cancer in Japanese women cannot be explained by smoking alone. The proportion of smokers among Japanese women remained around 15% during the last thirty years (Tominaga 1982) and the most predominant histologic type of lung cancer among them was adenocarcinoma, which was considered to be more weakly associated with smoking as compared to lung cancer of other cell types (Shimizu 1983; Nakamura et al. 1986; Shimizu et al. 1986).

Several studies have been conducted with emphasis laid on passive smoking and lung cancer since the first positive results were presented by Hirayama (1981) and Trichopoulos et al. (1981). Some of these studies showed a clear association of passive smoking with lung cancer (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986; Inoue et al. 1986). However, the results of other studies were equivocal or negative (Garfinkel 1981; Kabat and Wynder 1984; Koo et al. 1984; Wu et al. 1985; Lee et al. 1986).

This paper reports a case-control study of lung cancer in Japanese nonsmoking women, in which passive smoking and other factors such as occupational history, domestic heating system and dietary habits were investigated.

Materials and Methods

Our cases consisted of female patients with primary lung cancer who were treated in 4 hospitals in Nagoya from August 1982 to July 1985. One of the hospitals (Aichi Cancer Center Hospital) was a cancer hospital and the remaining three were general hospitals. Nagoya is the fourth largest city in Japan with a population of 2.1 million and located in the middle of the main island, Honshu.

During the above period 118 female lung cancer patients were pathologically identified. The physicians or nurses asked all of them to fill in a questionnaire for this study on the first or second day of admission to the hospitals. Out of 118 lung cancer patients 4 refused to fill in the questionnaire and 24 reported that they were current or exsmokers. The remaining 90 nonsmoking patients were selected as the cases for the following analyses. The questionnaire mainly consisted of the questions about smoking, occupational history, dietary habits, personal disease history and about the kinds of fuel for cooking. As regards passive smoking, we asked them about the smoking habits or the number of cigarettes smoked per day by parents, siblings, children or husband's parents in the home. We also asked them about the length of time which the woman spent with her husband in the same room, the period of married life and the number of cigarettes smoked by her husband. The passive smoke exposure at working places was assessed only in terms of the presence or absence of smokers. As regards dietary history, we asked the frequency in recent five years of intake of food items and divided into four categories (no intake, 1 or 2 days/week, 3 or 4 days/week, and almost every day). We asked directly the number of glasses of milk and the number of oranges taken per week.

The 90 lung cancers included 69 adenocarcinomas (77%), 13 squamous cell carcinomas (14%), 4 large cell carcinomas (4%), 3 small cell carcinoma (3%) and 1 adenoid cystic carcinoma (1%). The number of cases in the age group of 30-39, 40-49, 50-59, 60-69, 70-79 and 80+ years were 3 (3%), 16 (17%), 28 (31%), 27 (30%), 14 (16%) and 2 (2%) respectively. The minimum and maximum ages of the cases were 35 and 81 years and those

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of controls were also 35 and 81 years, respectively. The mean age at admission was 59 years for cases and 58 years for controls.

As a control, we asked female in-patients other than those with lung cancer in the same or adjacent wards of the hospital to fill in the questionnaire as we did for lung cancer patients (i.e., potential controls). We selected two controls matched in terms of hospital (the same hospital), age (±1 year), and date of admission for each case from these potential controls. For 17 cases we could find only one control which satisfied the criteria. The controls finally used for this analysis comprised 163 patients with the following diseases: breast cancer 67, (41%); diabetes mellitus, 11 (7%); stomach cancer, 11 (7%); hepatitis and other liver diseases, 8 (5%); malignant lymphoma, 7 (4%); heart diseases 5, (3%); hypertension 5, (3%); gall stone, 4 (2%); colorectal cancer 3, (2%); cancer of the uterine cervix 3, (2%); and others 39, (24%).

The logistic regression method was applied to this individually matched case-control study and odds ratio was computed as estimated relative risk for each variable (Breslow et al. 1978; Breslow and Day 1980). The statistical significance was determined by using two-sided p values.

Results

Table 1 shows the risk of female lung cancer for several types of passive smoking. When the mother of a case was a smoker, the relative risk of lung cancer was 4.0 ($p<0.05$). However, the risk was not elevated when her father was a smoker (RR = 1.1). High relative risk was observed when the husband's father living with the case smoked in the home (RR = 3.2; $p<0.05$). When mother or husband's father was a smoker, the relative risk was 3.3 ($p<0.01$). There was no association between the risk of lung cancer and smoking by husband, siblings or children in the home.

Passive smoke exposure at work was not clearly associated with female lung cancer, although the relative risk was slightly elevated (RR = 1.2).

Table 2 shows the combined effect of household smoking by mother and

Table 1. *Relative risks (RR) of lung cancer in nonsmoking women for serveral types of tobacco smoke exposure*

Smoker	Frequency in controls (%)	RR
In the home:		
Husband	56	1.1
Father	41	1.1
Mother	3	4.0*
Husband's father	8	3.2*
Husband's mother	4	0.8
Son(s) or daughter(s)	40	0.8
Brother(s) or sister(s)	32	0.8
Someone at working place	35	1.2

*$p<0.05$.

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TABLE 2. *Relative risks of lung cancer in nonsmoking women for smoking by mother and husband's father in the home*

		Smoking by husband's father	
		(−)	(+)
Smoking by mother	(−)	1.0	3.9*
	(+)	6.3	2.8

*$p < 0.05$

husband's father. Both of these two variables showed a relatively high risk independently. Particularly, the risk for smoking by husband's father in the absence of smoking by mother was significantly elevated (RR=3.9, $p < 0.05$). However, no synergistic effect of the above two variables was observed.

About 60% of the respondents had occupations. No difference was found in the distribution of the occupational categories between cases and controls. However, histories of occupational exposure to specific substances showed high risks of lung cancer. The relative risk for exposure to iron or other metals was 4.8 ($p < 0.05$), although the frequency of such exposure was very low in controls. The relative risk for exposure to coal, stone, cement, asbestos or ceramics was 3.3, but it was not statistically significant.

For the analysis of dietary habits, cut points dividing into lower two and higher two categories are arbitrarily chosen in general. We selected the 8/week or more as cutpoint for mandarine oranges in winter and odds ratio of milk was computed for the daily intake. Table 3 shows that there is neither positive nor negative association with food items investigated here. Only chicken showed the low risk of 0.7. We observed no dose-response relationship for these variables.

The personal medical history of silicosis showed the relataive risk of 2.0, but

TABLE 3. *Relative risks (RR) of lung cancer in nonsmoking women in relation to the frequency of food intake*

Food item	Frequency of intake	Frequency of intake in controls (%)	RR
Green-yellow vegetables	≥3 d w	86	0.9
Fruit	≥3 d w	86	1.2
Oranges (mandarine)	≥8 w	77	1.0
Milk	≥1 glass/d	76	1.0
Fish	≥3 d w	55	1.0
Pork	≥3 d w	22	1.0
Beef	≥3 d w	20	1.0
Chicken	≥3 d w	40	0.7

d, days; w, weeks.

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TABLE 4. *Relative risks (RR) of lung cancer in nonsmoking women for type of household heating system used in recent years*

Type of household heating system	Frequency in controls (%)	RR
Gas	32	1.0
Kerosene	86	1.6
Coal or charcoal	8	1.7

TABLE 5. *Relative risks (RR) of lung cancer in nonsmoking women in relation to the selected factors (n = 65)*

Factor	RR	
	Crude	Adjusted†
Smoking by mother in the home	3.0	2.1
Smoking by husband's father in the home	3.5*	3.2*
Occupational exposure to iron or other metals	2.8	2.4

†RR of each factor adjusted for other two factors after excluding the pairs in which one of the factors had unknown values.

*$p < 0.05$.

it was not statistically significant. The risk for histories of both chronic bronchitis and asthma was 0.8, and the risk for history of tuberculosis was 1.1.

No appreciable difference was observed between cases and controls in the type of household heating in childhood and in the kinds of fuel for cooking in adulthood. However, a recent use of a kerosene or coal (charcoal) stove for household heating showed a somewhat higher risk (RR = 1.6 and 1.7, respectively). However, neither of them was statistically significant (Table 4).

The frequency of using cooking oil was almost the same in cases and controls.

To confirm the risk associated with each variable described above, we computed the relative risk by using the multiple logistic regression analysis for the main 3 variables. Table 5 shows that the results are almost the same as those in univariate analysis.

Discussion

The presence of a smoking family member does not necessarily indicate that exposure to a sidestream of cigarettes has actually occurred. To know the level of passive smoking, measurement of concentration of cotinine in the urine is useful (Matsukura et al. 1984; Wald et al. 1984). However, it is very hard to assess the passive smoking level over a period of several decades because the half-life of serum cotinine is 72 hr. In this analysis we used only the information on smoking history of the respondents, their family members and their colleagues at working

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places.

In this study we found a positive association between lung cancer in nonsmoking women and the smoking history of family members, especially that of mother and husband's father. As Japanese children usually spend much longer time with their mother than other family members do, mother's smoking may be a representative index of passive smoking before leaving home at around 20 years of age. Recently we found that the saliva cotinine level of nonsmoking schoolchildren is not high when their fathers were smokers but high when their mothers were smokers in Miyagi, a district of northeastern Japan (unpublished data). After marriage, 35% of women in controls lived with their husband's parents. The final proportion of control women whose husband's father smoked cigarettes in the home was as small as 8%, but that (18%) of cases was somewhat larger. The husband's father may have retired already and may have stayed home much longer than the husbands. There is a possibility that Japanese women may be more frequently exposed to the smoke of cigarettes by their husband's father than that by their husband.

We assessed the total length of period which a woman spent with her husband from the length of the period of marriage and the hours during which she lived in the same room, but no difference was found between cases and controls.

No dose-response relationship was observed between the risk of lung cancer and the history of smoking of mother or husband's father. Usually the respondents remember whether their mother or their husband's father were smokers, but they may be unable to recall the exact number of cigarettes smoked by their mother (especially in childhood) or husband's father in the home.

It has been suggested that beta-carotene and preformed vitamin A decrease the risk of lung cancer (Smith 1982; Hinds et al. 1984). We asked a very simple question concerning the frequency of green-yellow vegetable intake, which has been referred to as a protective factor against lung cancer in a large cohort study of Japan (Hirayama 1982). No association was observed between this variable and female lung cancer risk in our study. Most of the respondents had green-yellow vegetables very frequently and we found no difference between cases and controls. There was no dose-response relationship between the frequency of intake of green-yellow vegetables and lung cancer risk.

We also assessed the efficacy of vitamin supplements over a period of more than one year in this analysis, and found the risk of 0.5. However it was not statistically significant.

Other dietay factor such as vitamin C and cholesterol may be related to the development of lung cancer (Hinds et al. 1983, 1984; Byers and Graham 1984), but no appreciable association was observed between the risk of lung cancer and the intake of food items listed in this study. To evaluate the effect of dietary habits, more precise measurement of food intake is needed.

A slightly elevated risk for disease history of silicosis is consistent with the

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data in recent reports (Finkelstein et al. 1982; Lynge et al. 1986), despite the fact that our results were based on the information reported by the respondents and that the number of cases with silicosis was very small. An excess risk of adenocarcinoma of the lung was observed previously for those with occupational exposure to iron or other metals in Nagoya area (Shimizu 1983). Even if the risk for these occupational exposure is confirmed, contribution of these factors is small because the frequency of such exposure is very low in Japan.

Possibly there is some bias in our study. Lung cancer cases were not derived from general population but from the patients of a limited number of hospitals. The proportion of adenocarcinoma patients in our series was ten percent larger as compared with that in total lung cancer patients of this area. The proportion of squamous cell carcinoma showed an opposite tendency (Karasawa 1985). We selected the controls from the same hospitals considering that both cases and controls in the same hospital may have similar backgrounds. However, one of the hospital was a cancer hospital and we had to include many breast cancer patients in the controls. For this reason we compared the status of passive smoking among the breast cancer patients with that among other controls, but we found no difference. Furthermore, the risk of lung cancer for the survivors of cancer of the breast was not high when assessed by the data of a population-based cancer registry (Takano and Okuno; personal communication).

Our study showed that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. As the precise situation of passive smoking in the home or other places is still unclear, further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

Acknowledgments

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Svensson, C., Pershagen, G. and Klominek, J., "Smoking and Passive Smoking in Relation to Lung Cancer in Women," Acta Oncologica 28(5): 623-629, 1989.

In this population-based case-control study, conducted in Stockholm county, Sweden, 210 cases and 209 age-matched population controls were questioned via interview. The study's purpose was to investigate "the association between female lung cancer and some possible etiological agents." Cases were identified in the area's major hospitals; controls were chosen at random from the county population register. For the ETS analyses, a hospital control group was sometimes included as well; this group consisted of women with suspected lung cancer who had been investigated and found not to have lung cancer. Questions included in the interview concerned diet, "exposure to ETS" (including domestic exposure during childhood and adult domestic and workplace exposure), smoking, and residential history. All but two of the cases were histologically or cytologically confirmed; carcinoids and unconfirmed cases were excluded from the ETS analyses.

No statistically significant RRs for ETS exposure indices were reported in never-smoking women; only 38 of the 210 cases had never smoked. Two indices assessing "lifetime exposure" were presented: exposed as child or adult RR = 1.4 (95% CI 0.2-2.5), and exposed as child and adult RR = 1.9 (95% CI 0.2-3.7). Regarding childhood exposure, for father smoking during childhood, an overall RR of 0.9 (95% CI 0.4-2.3) was reported; for mother smoking during childhood (only 3 cases), the reported RR = 3.3 (95% CI 0.5-18.8). Workplace exposure was not discussed separately, rather, the authors presented two indices: exposure as adult at home or at work, RR = 1.2 (95% CI 0.4-2.9), and exposure as adult at home and at work, RR = 2.1 (95% CI 0.6-8.1).

Although diet was included in the questionnaire, it was not discussed in the publication.

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FROM THE DEPARTMENT OF CANCER EPIDEMIOLOGY, RADIUMHEMMET, THE DEPARTMENT OF EPIDEMIOLOGY, INSTITUTE OF ENVIRONMENTAL MEDICINE, KAROLINSKA INSTITUTE, STOCKHOLM, AND THE DEPARTMENT OF LUNG MEDICINE, HUDDINGE HOSPITAL, HUDDINGE, SWEDEN.

SMOKING AND PASSIVE SMOKING IN RELATION TO LUNG CANCER IN WOMEN

C. SVENSSON, G. PERSHAGEN and J. KLOMINEK

Abstract

In a population based case-control study the association between female lung cancer and some possible etiological agents was investigated; 210 incident cases in Stockholm county, Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative risks for those who had smoked daily during at least one year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose–response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have implications for risk assessments regarding passive smoking.

Key words: Lung carcinoma, smoking, environmental tobacco smoke, case-control.

Carcinoma of the bronchi and lungs (lung cancer) is a common and highly lethal malignant disease. The dominating role of smoking as causative factor is established through numerous studies. The incidence is generally much higher among men, but in the USA lung cancer is now replacing breast cancer as the leading cause of cancer mortality among women (1). Among Swedish women the trend for annual increase of lung cancer is second only to malignant melanoma of the skin (2).

Many studies have shown that adenocarcinoma constitutes a greater proportion of the lung cancer incidence in females than in males (3). The difference can partly be explained by differences in smoking habits between the genders, but there are some indications that a similar pattern can be seen in non-smokers (4, 5).

During the last few years several studies have indicated that 'passive smoking' or exposure to environmental tobacco smoke (ETS) may be of etiological importance. The findings have recently been evaluated (6). Most of the studies have focussed on the effects of ETS exposure during adulthood, but some data suggest an effect of childhood exposure both in smokers and non-smokers (7, 8).

To further investigate the effects on women of smoking and other possible etiological factors for lung cancer, such as ETS and radon exposure in the home, and possible protective effects of some dietary components, we performed a population based case-control study. The first part of the study, addressing the risks associated with smoking and ETS, is presented in this paper.

Material and Methods

The study included Swedish-speaking women living in Stockholm county between 1983 and 1986. Persons in the county with suspected or newly detected lung cancer are as a rule referred to one of three clinical departments of lung medicine (Karolinska, Huddinge, and Södersjukhuset), or to the Department of Thoracic Surgery (Karo-

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linska) for further investigation and/or treatment. To be included in the present study, the subjects should be in a physical and mental condition that allowed an interview lasting between one half to one hour.

Suspected and confirmed cases were interviewed in the hospital wards. For inclusion in the study the diagnosis should be confirmed microscopically or by unambiguous chest radiograms in conjunction with a typical clinical course. The majority of interviews were made before the diagnosis was confirmed. When a case was confirmed and included in the study, a population control born on the same day was chosen at random from the population register in Stockholm county. If she could not be traced or refused to participate, she was replaced by another woman, who was selected and contacted in the same manner. The controls were interviewed by the same persons that interviewed the cases. The control interviews were made during a personal visit (58%) or by telephone.

A hospital control group was also included in some of the analyses pertaining to ETS-exposure. This group was selected among those patients with suspected lung cancer who were interviewed, but for whom the subsequent investigation ruled out this diagnosis.

The cases and hospital controls were interviewed during September 1983–December 1985. The last population control was interviewed one year later. The time lag between interviews of cases and population controls was mainly caused by the interval between admittance of a patient to a clinic and definite confirmation or rejection of the preliminary diagnosis. Eighty-six percent of the study subjects were interviewed by two physicians (CS and JK). The remaining subjects were interviewed by two other physicians.

A structured questionnaire was used for the interviews. It contained questions about frequency of consumption of food-stuffs rich in vitamin A, carotenoids, and vitamin C, exposure to ETS, smoking, and data on all dwellings in which a subject had lived for more than two years continuously. Exposure to ETS was assessed through questions about domestic exposure during childhood as well as domestic and work environment exposure during adult life. The criterion for being classified as a smoker was that the subject should have smoked daily for at least one year.

Statistical evaluation was made with the computer program EPILOG (9). Relative risks (rate ratios) were mainly estimated by stratified analyses with the extension for trend of the Mantel-Haenszel procedure (10, 11). In the trend analysis the exposures were scored 1, 2, 3, etc. In the matched analyses the exact method for computing confidence intervals (CI) described by Miettinen was used (12). In the unmatched analyses Cornfield's method was used (13). For some of the analyses multiple logistic regression models were used as well (14). Significance intervals presented in the article are two-sided and 95% CI are used throughout.

Results

The study finally included 210 cases and 209 population controls. In addition, 191 interviewed patients were shown not to have lung cancer. For 9 patients primary lung cancer could neither be confirmed nor excluded. Seven subjects refused interview and 5 could not be interviewed because of their medical condition.

One hundred and seventy-five (84%) of the population controls were first hand choices. One control did not have a corresponding case, since the case had to be excluded during the analysis, when an autopsy revealed primary carcinoma of the colon with pulmonary metastases and not primary lung cancer. For two cases no controls willing to be interviewed were found.

Table 1 shows the microscopical classification of the cases. All but two were histologically or cytologically confirmed. In one of these an autopsy showed characteristic macroscopical changes of malignant nature, but unfortunately a microscopical investigation was not made. Adenocarcinoma was most common and constituted approximately one-third of the cases. The age distribution was similar in the different histological groups.

Table 2 displays the diagnoses for the non-lung cancer patients along with their smoking status. Malignant disease other than lung cancer was the most common cause and constituted approximately one-fourth of this group of patients. An additional 17 patients in this group had a malignant disease although not directly associated with their respiratory ailments and consequently not the reason for their hospitalization. Table 2 also shows that the proportion of smokers among the population controls was smaller than for the non-lung cancer patients.

Smoking. All analyses pertaining to smoking were made using the population controls only. The relative risk for lung cancer for those who had ever smoked vs. never-smokers was calculated both in a matched analysis and in an unmatched analysis adjusted for age. The two methods yielded similar results, e.g. the risk estimate for all lung cancers was 5.8 (CI: 3.4–10.3) in the matched analysis and 6.4 (CI: 4.0–10.5) in the unmatched. The highest risk was seen for small cell cancer (33.7, unmatched) and the lowest for adenocarcinoma (3.1, unmatched). The mean age for the cases, who were never-smokers, was higher than for those who had ever smoked (66.3 vs. 61.7, $p=0.009$).

Table 3 shows the dose-response relationships for different types of lung cancer with average daily cigarette consumption as exposure variable. Subjects who had stopped smoking more than two years prior to the interview (for population controls two years before the interview of the corresponding case) were classified as ex-smokers. Small cell and squamous cell carcinomas showed the strongest trend of increasing relative risk with increasing smoking intensity. For some of the estimates the CI was very wide because of the small number of never-smokers among the cases, especially among those

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Table 1

Lung cancer cases among women in Stockholm county according to histological type of tumor and diagnostic verification

	Histol. evidence		Cytol. evidence		No microsc. evidence		Total		Mean age (years)
	n	%	n	%	n	%	n	%	
All cases	148	70.5	60	28.6	2	1.0	210	100.0	62.5
Squamous cell	41	77.4	12	22.6	0	0.0	53	25.2	63.7
Small cell	30	66.7	15	33.3	0	0.0	45	21.4	62.6
Adeno	55	76.4	17	23.6	0	0.0	72	34.3	61.6
Other	22	55.0	16	40.0	2	5.0	40	19.0	62.3

Table 2

Diagnoses and smoking among female non-lung cancer patients interviewed at departments for pulmonary diseases in Stockholm county as well as proportion of smokers among population controls

Diagnosis	n	%	Smokers %
Malignant tumor	47	24.6	59.6
Breast	13	6.8	46.2
Gynecological	11	5.8	54.5
Pneumonia or other respiratory infection	35	18.3	54.3
Unspecified pulmonary infiltration	23	12.0	65.2
Benign tumor or cyst	22	11.5	40.9
Pleuritis	8	4.2	50.0
Tuberculosis	5	2.6	60.0
Sarcoidosis	5	2.6	20.0
Haemoptysis	5	2.6	100.0
Chronic bronchitis	5	2.6	100.0
Bronchiectasis	4	2.1	75.0
Atelectasis	4	2.1	25.0
Other specified diagnosis	24	12.6	67.0
Unspecified diagnosis	4	2.1	50.0
Total	191		58.1
Population controls	209		42.6

with squamous or small cell cancer. Nevertheless, the lower limit of the CI was 2.9 and 6.9 respectively for the lowest smoking category within these groups of cancer. Only one control belonged to the highest exposure category, why the risk estimates for this category became very imprecise.

Average daily consumption of cigarettes was highly correlated to cumulated smoking ($r=0.90$, CI: 0.88–0.92) and to duration of the smoking habit ($r=0.73$, CI: 0.68–0.77). As a consequence of the high correlations the dose–response relationships were similar for these exposure measures.

The influence of the age at debut of daily smoking on relative risk is shown in Table 4. The risks are adjusted for duration of smoking. No statistically significant association could be found between smoking debut and risk although almost all point estimates of relative risk were higher for those starting before 25 years of age than after. Analyses were also made with simultaneous adjustments for age and intensity of smoking. The results were similar in both types of analysis, although the risk estimates were somewhat higher when the latter type of standardization was used. This could be expected as persons with an early debut also had a higher cumulated exposure within each age stratum. Other age stratifications were analysed, but the results were similar to those presented.

The effect of smoking cessation on relative risk of lung cancer is shown in Table 5. Few subjects, especially among the cases, with an average daily consumption of more than 10 cigarettes had ceased to smoke. The data indicated a considerable decrease in risk already within 10 years of smoking cessation compared to continued smoking. There seemed to be a stronger effect of smoking cessation for squamous and small cell carcinomas than for the other histological types.

Environmental tobacco smoke. Risk estimates of lung cancer associated with ETS were mainly calculated for cases and controls who had never been daily smokers, but for exposure to ETS during childhood calculations were also made for smokers. To increase power, the risk estimates presented for never-smokers were calculated with an expanded control group consisting of population controls and those non-lung cancer patients, who did not have any malignancy. The estimates arrived at when using only the population controls were quite similar. The carcinoids and the microscopically unconfirmed cases were excluded from the risk calculations pertaining to ETS.

Table 6 shows estimates of relative risk for smokers associated with exposure to ETS from the parents. Subjects with a smoking father only, were classified as exposed to low levels while subjects with a smoking mother were classified as exposed to high levels regardless of the smoking status of the father. No significantly increased relative risk was seen in any of the exposure groups.

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Table 3

Relative risk (RR) for lung cancer among women in Stockholm county in relation to average daily cigarette consumption[1]

	Never-smokers	Ex-smokers		Current smokers						p for trend[2]
	n	n	RR (95% CI)	>0–10 cig/day		>10–20 cig/day		>20 cig/day		
				n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)[3]	
All cases	38	30	2.6 (1.4–5.1)	42	4.6 (2.5–9.3)	81	12.6 (6.5–25.2)	19	59.0 (7.6–)	$<1.4\times10^{-22}$
Squamous cell	5	6	4.0 (1.0–16.9)	10	9.7 (2.9–45.9)	28	36.2 (12.0–168.9)	4	96.0 (6.9–)	$<3.8\times10^{-16}$
Small cell	2	5	9.1 (1.4–69.7)	13	33.7 (6.9–265.3)	20	72.1 (11.9–452.6)	5	215.8 (18.3–)	$<1.8\times10^{-16}$
Adeno	22	12	1.8 (0.8–4.3)	12	2.2 (1.0–5.8)	22	5.4 (2.4–13.2)	4	19.7 (1.7–)	$<1.7\times10^{-7}$
Other	9	7	2.5 (0.8–8.1)	7	3.6 (1.1–13.4)	11	7.5 (2.2–24.3)	6	82.5 (7.6–)	$<8.0\times10^{-9}$
Controls	120	36		30		22		1		

[1] The estimates are adjusted for age. Subjects who had stopped smoking more than 2 years before the interview (for controls 2 years before the interview of the matched case) are classified as ex-smokers.
[2] Ex-smokers not included in calculations of linear trend. The exposures were scored 1, 2, 3 and 4.
[3] Upper confidence intervals not given because of imprecision of estimates due to the small number of individuals in the high exposure stratum.

Table 4

Relative risk (RR) for lung cancer among women in Stockholm county associated with age at debute of daily smoking[1]

	>25 years	19–25 years		–18 years		p for trend[2]
	n	n	RR (95% CI)	n	RR (95% CI)	
All cases	32	58	2.0 (0.8–5.3)	52	1.2 (0.5–2.8)	0.9
Squamous cell	9	18	2.0 (0.6–7.3)	15	1.1 (0.3–3.8)	0.9
Small cell	7	18	2.2 (0.6–8.4)	13	1.3 (0.4–4.9)	0.9
Adeno	10	11	1.6 (0.4–6.0)	17	1.3 (0.4–4.4)	0.6
Other	6	11	2.2 (0.5–9.9)	7	1.0 (0.2–4.2)	0.7
Controls	18	14		21		

[1] Stratified analysis adjusted for duration of smoking. Subjects who had stopped smoking more than 2 years before the interview (for controls 2 years before the interview of the matched case) are excluded.
[2] The exposures were scored 1, 2 and 3.

although all risk estimates exceeded 1.0 in women with smoking mothers.

In never-smokers, adenocarcinoma constituted the dominating histological group with 22 (57.9%) of the total of 38 carcinomas. There were only 5 squamous cell and 2 small cell carcinomas, making specific analyses of these histological groups unfeasible.

Table 7 shows risk estimates for different ETS exposure variables among never-smokers. Most of the point estimates of the relative risk were greater than unity but the CI were wide due to the small number of cases. There were no significant trends. Multiple regression analysis yielded risk estimates very similar to those presented in the table.

There was a significantly increased 'risk' of being exposed to ETS in the home, if the subject herself was a

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Table 5

Relative risk (RR) for lung cancer among women in Stockholm county associated with smoking cessation (sc) compared to current smoking (0–2 years after cessation).[1]

	Current smoking n	3–10 years since cessation		>10 years since cessation		p for trend[2]
		n	RR (95% CI)	n	RR (95% CI)	
All cases	142	16	0.6 (0.2–1.4)	14	0.3 (0.1–0.6)	0.0004
Squamous cell	42	5	0.5 (0.1–1.6)	1	0.0 (0.0–0.4)	0.0006
Small cell	38	2	0.3 (0.0–1.3)	3	0.2 (0.0–0.7)	0.001
Adeno	38	5	0.5 (0.1–1.7)	7	0.5 (0.2–1.5)	0.06
Other	24	4	0.7 (0.2–3.2)	3	0.4 (0.1–1.6)	0.08
Controls	52	13		24		

[1] Stratified analysis adjusted for age and average daily cigarette consumption.
[2] The exposures were scored 1, 2 and 3.

Table 6

Relative risk (RR) for lung cancer among ever smoking women in Stockholm county in relation to parental smoking during the first decade of life[1]

	Unexposed n	Father smoker		Mother smoker[2]		p for trend[3]
		n	RR (95% CI)	n	RR (95% CI)	
All cases	94	57	0.8 (0.3–1.4)	19	1.8 (0.5–7.0)	0.9
Squamous cell	27	17	0.7 (0.3–1.7)	4	1.3 (0.2–8.8)	0.6
Small cell	25	13	0.7 (0.3–1.8)	5	2.1 (0.3–14.0)	1.0
Adeno	23	19	1.1 (0.5–2.5)	8	3.0 (0.6–21.6)	0.3
Other	19	8	0.4 (0.1–1.3)	2	1.1 (0.0–20.0)	0.08
Controls	45	39		5		

[1] Stratified analysis adjusted for age and average daily cigarette consumption.
[2] Regardless of smoking habits of the father.
[3] The exposures were scored 1, 2 and 3.

smoker. The point estimate for cases was 4.0 (CI: 1.7–9.3) and for controls 3.0 (CI: 1.5–6.2). For controls there was also a significantly increased 'risk' of being exposed to ETS on the job if the subject had ever smoked (RR 1.9, CI: 1.0–3.7). For cases the corresponding point estimate was 1.1 (CI: 0.5–2.6).

Discussion

All subgroups of lung cancer were strongly associated with smoking. Due to the small number of never-smokers among the cases, especially among squamous and small cell cancers, and of heavy smokers among the controls, the confidence intervals were wide. The magnitudes of the risk estimates were greater than, but not incompatible with, results from previously published studies on female lung cancer (15–18).

Contrary to previous studies (15, 17, 19) no clear association between early smoking debut and risk was seen, although most of the point estimates were greater than unity when smoking debut after age 25 was used as reference category. In light of the clear dose–response rela-

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Table 7

Relative risk (RR) for lung cancer among never smoking women in Stockholm county in relation to different measures of exposure to ETS[1]

	Cases	Controls	RR	95% CI
Exposure from the parents[2]				
Unexposed	19	98	1.0	
Father smoker	12	71	0.9	0.4–2.3
Mother smoker	3	5	3.3	0.5–18.8
		(p for trend[3]: 0.6)		
Exposure as adult				
Unexposed	10	60	1.0	
At home or at work	17	90	1.2	0.4–2.9
At home and at work	7	24	2.1	0.6–8.1
		(p for trend[3]: 0.4)		
Lifetime exposure				
Unexposed	7	35	1.0	
As child[2] or adult	15	88	1.4	0.2–2.5
As child[2] and adult	12	51	1.9	0.2–3.7
		(p for trend[3]: 0.5)		

[1] Stratified analysis adjusted for age.
[2] Age 0–9 years.
[3] The exposures were scored 1, 2 and 3.

tionships in the other studies as well as in studies on men, the present findings were unexpected. A possible explanation could be that those who started to smoke at a younger age inhaled less deeply or that they to a greater extent smoked cigarettes with filter tips. The observed decrease in the relative risk of lung cancer after smoking cessation is in agreement with previous observations (16, 18, 20).

Approximately one-third of all cases were classified as adenocarcinoma. Among the never-smokers adenocarcinoma constituted almost 60% of the cases. Among the current smokers the corresponding figure was 27%. The proportion of adenocarcinoma among the never-smokers is in good agreement with several previous studies on female lung cancer (5, 16, 21–23).

The results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking (6, 24).

To reliably estimate the risk associated with ETS, it is essential to identify a sufficient number of never-smokers. In the present study, only 38 of the 210 cases had never been daily smokers. Four of these were excluded from the calculations of risks associated with ETS, since they had carcinoids or tumors which were not confirmed microscopically. A post hoc calculation of power for detecting a 50% excess risk associated with exposure to ETS in the home, showed that it was in fact only about 10%.

For detecting small risks, it is essential to minimize misclassification of exposure. The variables characterizing exposure to ETS used in this study may not be optimal in this respect. Both intensity and temporal aspects of the exposure are probably of importance for the outcome. It is very difficult, however, to retrospectively quantify ETS exposure. The tolerance for tobacco smoke differs between individuals, and it is not improbable that this can influence their exposure estimates. If such individual information bias exists, it is uncertain whether it leads to non-differential or systematic misclassification. There are also difficulties involved in assessing the relative importance of domestic exposure compared to exposure in the work environment.

The high risks found for smokers with a low consumption in this study, and particularly for squamous and small cell carcinomas, have implications for the assessment of lung cancer risks associated with ETS. On one hand, they suggest that relative risks of 3 or even higher for squamous and small cell carcinomas in heavily exposed individuals may not be unreasonable. On the other hand, they make control of confounding by smoking a critical issue. A poor control of confounding would be expected to primarily give rise to increased risks of these histological types.

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Request for reprints: Dr Christer Svensson, Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, P.O. Box 60208, S-104 01 Stockholm, Sweden.

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Janerich, D., Thompson, W.D., Varela, L.R., Greenwald, P., Chorost, S., Tucci, C., Zaman, M.B., Melamed, M.R., Kiely, M. and McKneally, M.F., "Lung Cancer and Exposure to Tobacco Smoke in the Household," The New England Journal of Medicine 323: 632-636, 1990.

Note: This is the published report on the Varela doctoral dissertation.

This case-control study concerns a subset (191 cases, 191 controls) of the original study, and reanalyzes the data in new ways. The authors state their hypothesis as "to further clarify the role of passive smoking in lung cancer." A total of 191 cases and 191 controls were included in this report. Cases were ascertained using a hospital-based reporting system in New York State; all were histologically confirmed. Controls were identified using the New York State Department of Motor Vehicles registry, and were matched on age, sex, county of residence and smoking history. Although 32.5% of the interviews were with proxy respondents, cases and controls were also matched as to interview type.

A great number of RR estimates were calculated by the authors. One statistically significant estimate was reported: for at least 25 smoker-years exposure during childhood and adolescence (up to age 21), RR = 2.07 (95% CI 1.16-3.68). For spousal smoking status, the reported RR was 0.93 (95% CI 0.55-1.57). For exposure of 150 person-years in the workplace, a RR of 0.91 (95% CI 0.80-1.04) was calculated. The authors said there was "no evidence of an adverse effect." An inverse association with ETS exposure in social settings was reported.

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LUNG CANCER AND EXPOSURE TO TOBACCO SMOKE IN THE HOUSEHOLD

DWIGHT T. JANERICH, D.D.S., M.P.H., W. DOUGLAS THOMPSON, PH.D., LUIS R. VARELA, M.D., PH.D.,* PETER GREENWALD, M.D., DR.P.H., SHERRY CHOROST, M.S., CATHY TUCCI, B.S., MUHAMMAD B. ZAMAN, M.D., MYRON R. MELAMED, M.D., MAUREEN KIELY, R.N., AND MARTIN F. MCKNEALLY, M.D.

Abstract *Background.* The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

Methods. In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case–control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of "smoker-years," determined by multiplying the number of years in each residence by the number of smokers in the household.

Results. Household exposure to 25 or more smoker-years during childhood and adolescence doubled the risk of lung cancer (odds ratio, 2.07; 95 percent confidence interval, 1.16 to 3.68). Approximately 15 percent of the control subjects who had never smoked reported this level of exposure. Household exposure of less than 25 smoker-years during childhood and adolescence did not increase the risk of lung cancer. Exposure to a spouse's smoking, which constituted less than one third of total household exposure on average, was not associated with an increase in risk.

Conclusions. The possibility of recall bias and other methodologic problems may influence the results of case–control studies of environmental tobacco smoke. Nonetheless, our findings regarding exposure during early life suggest that approximately 17 percent of lung cancers among nonsmokers can be attributed to high levels of exposure to cigarette smoke during childhood and adolescence. (N Engl J Med 1990; 323:632-6.)

THE 1972 Surgeon General's report dealt with the health consequences of passive smoking or environmental tobacco smoke for the first time.[1] In 1986 the entire report was devoted to the issue; it concluded that "involuntary smoking is a cause of disease including lung cancer in healthy non-smokers."[2] More than a dozen epidemiologic studies have assessed the relation between passive smoking and lung cancer.[3-17] The findings have ranged from no detectable increase in risk[10,17] to a moderate (about twofold), statistically significant increase.[4-7] Most studies have found only small elevations in risk, which are frequently not statistically significant.[3,8,9] In a meta-analysis of all the available studies in 1986, Wald et al. found a slightly increased risk of lung cancer associated with environmental tobacco smoke.[18]

We undertook the current study in an attempt to clarify further the role of passive smoking in causing lung cancer. In this report we discuss exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers.

METHODS

We conducted a population-based, individually matched case–control study in New York State from 1982 to 1985. The cases were drawn from seven Standard Metropolitan Statistical Areas (Buffalo, Rochester, Syracuse, Utica–Rome, Albany–Schenectady–Troy, Binghamton, and greater New York, excluding the five boroughs of New York City). This geographic area comprises 23 counties, with approximately 125 diagnostic or treatment facilities, and a population base of nearly 10 million people. A special system for the rapid ascertainment of cases of lung cancer was established in these 125 facilities so that patients could be identified and enrolled as soon after diagnosis as possible. All new cases of lung cancer (diagnosed clinically, histologically, or both) were regularly identified at the participating hospitals. The New York State Cancer Registry was checked routinely to identify any cases that might have been missed by the hospital-based reporting system.

Information on smoking was initially obtained from the patients' medical records. All the case patients reported as having never smoked or as former smokers or whose smoking history was unknown were contacted by telephone, and their smoking status was confirmed. To be included as a "case" in the study, a patient had to reside in the 23-county area, be between 20 and 80 years of age, never have smoked more than 100 cigarettes (nonsmokers) or have smoked at some time but not have smoked more than 100 cigarettes in the 10 years before diagnosis (former smokers), and have been given a diagnosis of primary lung cancer between July 1, 1982, and December 31, 1984, that was confirmed on reexamination of the pathological specimens and clinical records. Slides or blocks of tissue were available for all but five of the case patients. All materials were reviewed by investigators who were blinded with respect to the patient's initial diagnosis, smoking history, and other risk factors. Interviews were conducted with 76 percent of the eligible patients or their closest available relatives or friends (surrogates).

Control subjects were individually matched to the patients and were selected by screening the files of the New York State Department of Motor Vehicles. This source of controls was considered appropriate since it was population-based and provided most of the information necessary to perform the matching. A list of potential control subjects for each case patient was selected on the basis of age (within five years), sex, and county of residence. Potential control subjects were contacted by telephone. The first eligible subject who was found to match the case patient in terms of smoking history (nonsmoker or former smoker) and who agreed to participate was enrolled in the study. An additional matching variable considered at the time of data collection was the type of interview — i.e., direct interview with the patient or control subject versus interview with a surrogate respondent. When a surrogate case patient had to be interviewed, we also interviewed a surrogate for his or her matched

From the Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn. (D.T.J.); the University of Southern Maine, Portland (W.D.T.); the Population Council of Mexico, Mexico City (L.V.R.); the National Cancer Institute, Washington, D.C. (P.G.); the New York State Department of Health, Albany (S.C., C.T.); the Sloan-Kettering Memorial Institute, New York (M.B.Z., M.R.M.); and Albany Medical College, Albany, N.Y. (M.K., M.F.M.). Address reprint requests to Dr. Janerich at the Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College St. (LEPH 105), New Haven, CT 06510.

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*Deceased.

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control, even when the control subject was available and willing to be interviewed. Further information on the methods used in the study is available elsewhere.[19]

Data were collected for 439 case–control pairs. Of these, 242 pairs were former smokers and 197 pairs had never smoked. Separating the residual effects of direct smoking from those of passive smoking among former smokers involves more complex analytic and interpretational issues than does an examination of the effects of passive smoking in those who have never smoked. This report is therefore limited to persons who never smoked. Six of the 197 pairs who had never smoked were mismatched in terms of the type of interview (direct vs. surrogate) and have therefore been excluded. Thus, the analyses reported here were based on 191 matched case–control pairs. A total of 129 pairs were interviewed directly, and surrogates were interviewed for 62.

All information was collected during a face-to-face interview with use of a precoded questionnaire. Case patients and control subjects were interviewed in exactly the same fashion, and except for items concerning the clinical aspects of the current medical condition, both groups answered the same questions.

Information about smoking in the household was collected separately for each residence in which the subject had lived for one year or more, up to a maximum of 12 residences. The number of "smoker-years" of exposure was calculated by multiplying the number of years the subject lived in each residence by the number of smokers (including the spouse) in that residence. The products for all residences were summed.

Smoking by the spouse was also recorded separately from that by other household members in a subsequent section of the questionnaire. The information consisted of the number of years the spouse had smoked while living with the case patient or control subject and the number of cigarettes smoked per day. Smoker-years of exposure from the spouse's smoking were calculated in the same manner as for the entire household. Pack-years of exposure from the spouse were calculated by multiplying the number of packs smoked per day by the number of years that the spouse smoked while living with the subject. If the subject had been married to more than one smoker, then the numbers of smoker-years and pack-years of exposure for all spouses were summed.

The questionnaire also included sections on exposure to environmental tobacco smoke in the workplace and in social settings outside the home. The format for these questions differed from that used to collect data on exposure in the household. The summary results of this analysis are presented here; detailed findings are available elsewhere.[19]

Statistical techniques appropriate for the analysis of individually matched case–control studies were used.[20] For clarity of presentation, percentages were tabulated for case patients and control subjects separately, rather than for matched pairs. However, odds ratios were computed on the basis of the matched pairs. The conditional logistic-regression model was used in the multivariate analyses.[20] Comparisons of the effects of exposures that occurred during different periods of the subjects' lives were based on evaluation of differences in the magnitude of appropriate logistic-regression coefficients. For statistical testing of these differences, we used the variance–covariance matrix from the logistic-regression analyses.

Results

Smoking by spouses contributed a large proportion of lifetime exposure to environmental tobacco smoke but was not the chief source of exposure. Table 1 shows the amount of exposure to environmental tobacco smoke (expressed in smoker-years) during childhood and adolescence, during adulthood, and from the spouse for the 191 control subjects who had never smoked. There were only small differences between men and women. The spouse contributed about 30 percent of the lifetime smoker-years of exposure; the correlation coefficients for exposure from the spouse and lifetime exposure were 0.37 for men and 0.51 for women. Exposure during childhood and adolescence (<21 years of age) contributed a similar percentage of the lifetime smoker-years but correlated more closely with lifetime exposure (correlation coefficient, 0.92 for men and 0.61 for women). The average lifetime exposure was 46.6 smoker-years for men and 52.7 smoker-years for women. During adulthood, household exposure from sources other than the spouse was somewhat greater than from the spouse.

Table 1. Distribution of Smoker-Years of Exposure to Environmental Tobacco in the Household.*

Category of Exposure	Men	Women
Lifetime smoker-years, mean ±SD	46.6±53.7	52.7±42.9
Smoker-years during childhood and adolescence†		
Mean ±SD	15.4±20.6	16.1±16.2
Percent of lifetime exposure	33.1	30.6
Correlation with lifetime exposure	0.92	0.61
Smoker-years from spouse		
Mean ±SD	13.0±17.0	16.2±16.7
Percent of lifetime exposure	28.0	30.7
Correlation with lifetime exposure	0.37	0.51
Smoker-years during adulthood from sources other than spouse		
Mean ±SD	18.1±31.0	20.5±29.9
Percent of lifetime exposure	38.9	38.9
Correlation with lifetime exposure	0.91	0.83

*Based on 45 male and 146 female control subjects who had never smoked more than 100 cigarettes. Information on smoker-years of exposure from the spouse is for 45 male and 140 female control subjects. Smoker-years were calculated by multiplying the number of years the subject lived in a residence by the number of smokers in the household.

†Less than 21 years of age.

Table 2 shows the odds ratios for developing lung cancer in relation to the degree of exposure to tobacco smoke in the household for the 191 nonsmoking case–control pairs. The data are stratified by levels of exposure (measured in smoker-years) and by the periods of life when the exposure occurred. Exposures during childhood and adolescence were defined as exposures that occurred when the subjects were less than 21 years of age. Exposures during adulthood include all household exposures from 21 years of age to the time of diagnosis. Although the odds ratios for the higher exposure categories are somewhat higher than those for the lower categories, no clear dose–response relation is evident, and most of the 95 percent confidence intervals include 1.0. For exposures in childhood and adolescence, the highest level of exposure is associated with the greatest elevation in risk, and the 95 percent confidence interval excludes the null value (odds ratio, 2.07; 95 percent confidence interval, 1.16 to 3.68). For the 129 case–control pairs who were interviewed directly, the odds ratio for persons with 25 or more smoker-years of exposure in childhood and adolescence was 2.31 (95 percent confidence interval, 1.16 to 4.61).

With smoker-years during childhood and adolescence and smoker-years during adulthood treated as continuous variables and included simultaneously in a logistic model, each increment of five smoker-years of exposure during childhood and adolescence was found to increase the risk of lung cancer by 6.5 percent (95 percent confidence interval, 0.1 to 13.2). On the other hand, each additional five smoker-years of exposure

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Table 2. Relation of Smoker-Years of Exposure to Environmental Tobacco Smoke to the Risk of Lung Cancer among Persons Who Never Smoked More than 100 Cigarettes.*

No. of Smoker-Years	Case Patients	Controls	Odds Ratio (95% CI)
	no. (%)		
Childhood and adolescence†			
0	57 (29.8)	68 (35.6)	—
1–24	82 (42.9)	94 (49.2)	1.09 (0.68–1.73)
≥25	52 (27.2)	29 (15.2)	2.07 (1.16–3.68)
Adulthood			
0	44 (23.0)	39 (20.4)	—
1–24	37 (19.4)	48 (25.1)	0.64 (0.34–1.21)
25–49	46 (24.1)	50 (26.2)	0.81 (0.45–1.45)
50–74	36 (18.9)	32 (16.8)	1.00 (0.52–1.93)
≥75	28 (14.7)	22 (11.5)	1.11 (0.56–2.20)
Lifetime			
0	32 (16.8)	33 (17.3)	—
1–24	20 (10.5)	27 (14.1)	0.78 (0.36–1.67)
25–49	35 (18.3)	46 (24.1)	0.80 (0.43–1.50)
50–74	44 (23.0)	40 (20.9)	1.19 (0.63–2.27)
75–99	33 (17.3)	21 (11.0)	1.80 (0.83–3.90)
≥100	27 (14.1)	24 (12.6)	1.13 (0.56–2.28)

*Based on 191 matched case–control pairs. CI denotes confidence interval. Odds ratios are shown for a person with the exposure specified as compared with a person with no exposure (0 smoker-years). Because of rounding, percentages do not always total 100.

†Less than 21 years of age.

during adulthood were estimated to have virtually no effect on risk (95 percent confidence interval, −3.3 to +2.8 percent). The difference in the magnitude of the effect between exposure during childhood and adolescence and exposure during adulthood did not achieve statistical significance ($P = 0.12$). On the basis of the distribution of exposure levels during childhood and adolescence among the control subjects and the magnitude of the effect of early exposure, we estimate that approximately 17 percent of all lung cancers in nonsmokers can be attributed to exposure to passive smoke in the household during childhood and adolescence. On the basis of the odds ratios for the 129 case–control pairs who were interviewed directly, approximately 19 percent of lung cancer in nonsmokers appears to be attributable to exposure to environmental cigarette smoke in childhood and adolescence.

Since smoking by the spouse has been the most commonly reported measure of exposure to environmental tobacco smoke in previous studies, we examined exposure from the spouse separately, although exposure to environmental tobacco smoke from the spouse is also included in the results shown in Table 2. The odds ratios for exposure frequently differed according to the type of interview, especially for the data on exposure to a spouse's smoking. Table 3 therefore shows the results of the analyses of exposure to environmental tobacco smoke from the spouse separately for subjects interviewed directly and those for whom surrogates were interviewed. The odds ratio for the development of lung cancer for those who ever had a spouse who smoked, as compared with those who did not, was 0.93 (95 percent confidence interval, 0.55 to 1.57) for those interviewed directly. In terms of smoker-years of exposure to the spouse's smoke, the results show little effect, with an odds ratio of 1.07 for 25 or more smoker-years of exposure (95 percent confidence interval, 0.59 to 1.97). Estimates based on pack-years of exposure from the spouse were similar to those based on smoker-years. For both measures, there was little evidence of a trend according to amount of exposure among those who were exposed.

All analyses were repeated for only the case–control pairs for whom we had complete and internally consistent data for all residences and marriages. Any pair was dropped from these analyses if data were incomplete or missing for either the case patient or the control subject, leaving 113 pairs of nonsmokers. Our purpose was to ensure that our conclusions were not dependent on the particular methods we adopted to handle inconsistencies or missing items in the data set. The findings were similar to those for the entire group of 191 pairs. The odds ratio for exposure to 25 or more smoker-years in childhood and adolescence was 2.59 (95 percent confidence interval, 1.22 to 5.49).

Exposure in the workplace was measured by recording the number of smokers who worked with each study subject during his or her lifetime and the amount of time the subjects spent working with these smokers. These exposures were compared for case patients and control subjects. Estimating the odds ratio as a continuous variable for an equivalent differential of 150 person-years of exposure gave an odds ratio of 0.91 (95 percent confidence interval, 0.80 to 1.04), indicating no evidence of an adverse effect of environmental tobacco smoke in the workplace. Our assessment of smoking in social settings used an untested, semiquantitative index in which the case patient or control subject used a score of 0 through 12 to indicate his or her regular exposure to tobacco smoke in social settings during each decade of life. Cumulative lifetime reported scores ranged from nearly 0 to more than 70. The odds ratio for an increase of 20 in the cumulative score was 0.59 (95 percent confidence interval, 0.43 to 0.81). Our analysis of exposure in social settings with use of this index showed a statistically significant inverse association between environmental tobacco smoke and lung cancer.

Discussion

We found a statistically significant adverse effect of relatively high levels of exposure to environmental tobacco smoke during the early decades of life (up to the age of 21). For those who were exposed to 25 or more smoker-years during their first two decades of life, the risk of lung cancer doubled. This amount of exposure is equivalent to living with more than one smoker throughout childhood and adolescence — a high but not uncommon level of exposure. An exposure of this level was reported for approximately 15 percent of the control group. By contrast, we found no adverse effect of exposure to environmental tobacco smoke during adulthood, including exposure to a spouse who

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Table 3. Relation of Spouse's Smoking to the Risk of Lung Cancer among Persons Who Never Smoked More than 100 Cigarettes, According to Type of Interview.*

VARIABLE	TYPE OF INTERVIEW	
	DIRECT	SURROGATE
	odds ratio (95% CI)	
Ever had a spouse who smoked		
No	—	—
Yes	0.93 (0.55–1.57)	0.44 (0.19–1.02)
Smoker-years of exposure from spouse		
0	—	—
1–24	0.78 (0.41–1.50)	0.33 (0.11–1.05)
≥25	1.07 (0.59–1.97)	0.33 (0.12–0.95)
Pack-years of exposure from spouse		
0	—	—
1–24	0.71 (0.37–1.35)	0.16 (0.04–0.62)
25–49	0.98 (0.47–2.05)	0.68 (0.18–2.60)
≥50	1.10 (0.47–2.56)	0.20 (0.03–1.22)

*Based on 129 case–control pairs interviewed directly and 59 pairs for whom surrogates were interviewed. Three of the 191 pairs were excluded because for one member of the pair there was missing information about whether the subject had a spouse who smoked. Data on smoker-years of exposure were available for 129 case–control pairs with direct interviews and 56 pairs with surrogate interviews. Data on pack-years of exposure were available for 122 pairs with direct interviews and 51 pairs with surrogate interviews. CI denotes confidence interval. Odds ratios are shown for a person with the exposure specified as compared with a person with no exposure to a spouse who smoked.

smoked. Although problems of recall and other potential biases may have influenced the results, our data suggest that exposure in early life may be a limited but important contributor to the risk of lung cancer in nonsmokers. A previous study with a small number of subjects found little evidence of an elevated risk of lung cancer among nonsmokers whose parents had smoked.[14] Children of parents who smoke have been shown to be especially susceptible to respiratory problems that occur soon after exposure to environmental tobacco smoke.[2] This type of susceptibility might initiate changes that eventually lead to lung cancer when the exposed children become adults, but we know of no specific mechanism that would explain our findings.

We found no adverse effects of exposure to tobacco smoke in the workplace, although we did not have enough information about the level of exposure in the workplace to assess the precision of our measurements. The apparent protective effect of exposure in social settings is difficult to explain. During the course of this study, regulations in New York began to restrict smoking in the workplace and in social settings such as restaurants. We did not anticipate this development and cannot estimate how much the awareness of these new restrictions might have affected the responses of the study subjects or their surrogates.

Evidence is clearly mounting that tobacco smoke inhaled passively by nonsmokers is potentially carcinogenic. In a recent study, Maclure et al.[21] found elevated levels of carcinogens in the blood of passive smokers. Levels of hemoglobin adducts of 4-aminobiphenyl and adducts of 3-aminobiphenyl were significantly elevated in subjects with confirmed exposure. The validity of this finding was supported by additional evidence that showed a sharp decline in the levels of adducts among smokers who quit.[21]

At present, information on past exposure to environmental tobacco smoke can be obtained only by interview. The available biologic markers, such as cotinine, cannot be used to confirm exposure that occurred years or decades earlier. The use of interviews to obtain a lifetime history of exposure to passive smoking requires that the questionnaire be structured and the interview techniques be standardized so that all subjects are interviewed in the same way. We took steps to ensure such standardization. Two recent reports may lead to improved ways to measure lifetime exposure to environmental tobacco smoke by means of interviews.[22,23] In one of these studies, which attempted to evaluate the reliability of interview data by repeat interviews, information on exposure during childhood was found to be very reliable.[23]

It was necessary to use surrogate respondents for about one third of the interviews, usually because the patients were too ill to be interviewed. To minimize potential bias, surrogates were also interviewed for the matched control subjects, and separate estimates were calculated for respondents interviewed directly and surrogate respondents. We used equal care in all types of interviews and in all subject areas covered in the interviews; however, the data we obtained in interviews with surrogates still differed somewhat from those obtained in direct interviews. Inaccurate reporting of exposure tends to bias odds ratios toward the null value unless a systematic bias is present. Data from surrogate respondents are likely to introduce random error because of the surrogate's lack of detailed knowledge of the subject's exposure. On the other hand, it is possible that the surrogates for patients with lung cancer might tend to underreport the exposure contributed by their own smoking to a greater extent than surrogates for control subjects. Such a difference could mask an actual increase in risk or reverse the direction of the association. The findings shown in Table 3 indicate that the use of data from surrogates may have led to an underestimation of the effect of exposure from the spouse. Although our results for exposure due to smoking by the spouse differ from those of earlier studies,[18] our findings regarding other types of household exposure support the conclusion that exposure to environmental tobacco smoke can cause lung cancer.

Akiba et al.,[8] Dalager et al.,[9] and Garfinkel[3] have reported elevations in risk of 30 percent, 50 percent, and 10 percent, respectively, associated with exposure to a spouse's smoking; none of these increases were statistically significant. With the exception of Chan et al.[24] and Koo et al.[25] in Hong Kong, these and most other investigators have reported point estimates that suggest an increased risk for those exposed. The duration of exposure, as measured by the number of years the spouse smoked while living with the subject, did not have a statistically significant effect in our data. Two studies that used the same measure

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of exposure also failed to exclude the null value.[8,9] Garfinkel et al.,[7] using a different measure for duration of exposure (husband's smoking in the last 5 and 25 years), found one significant association among the large number examined. Exposure due to smoking by the spouse, expressed in terms of pack-years while the spouse was living with the subject, was found not to be significantly associated with lung cancer. Using a comparable measure of exposure, Trichopoulos et al.[5] reported relatively large increases in risk (greater than twofold). Perhaps our data do not show that smoking by the spouse increased the risk by itself because smoking by the spouse made up only about one third of the subjects' lifetime exposure to environmental tobacco smoke. It is also possible that physical circumstances and differences in study areas, the size of residences, ventilation, and other important physical aspects of the living conditions, as well as social habits that affect exposure within the family, will need to be measured and analyzed before the differences in findings among the studies can be reconciled.

The evidence we report lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

We are indebted to Andreas Nicolaou for his assistance with the computer programming used in our analyses.

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Note: The Janerich, et al., (1990) paper is based on part of this otherwise unpublished study.

This large case-control study included 439 case-control pairs. Only histologically confirmed cases were included. It is one of the few studies actually designed to test the hypothesis that lung cancer risk in nonsmokers is associated with various indices of ETS exposure (e.g., spousal smoking). Cases and controls were matched by county of residence. While 33% of the interviews were with proxy respondents, cases and controls were matched on type of interview.

For spousal smoking, 73 statistical tests were run. None was statistically significant. Because of the large sample size of the study, the associated statistical power is high. For household exposure to ETS, measured in person/years, only one exposure level, ≥175 person/years had a statistically significant OR = 1.09. This is of marginal statistical significance when confounding factors are taken into account (lower CI of 1.00067). Of 27 analyses on workplace smoking, none was statistically significant. For ETS in social settings, no individual odds ratio was statistically significantly different from one, yet there was a highly significant inverse trend between ETS exposure and lung cancer risk.

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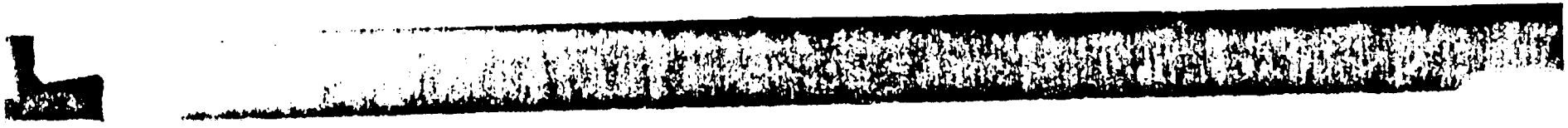

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ASSESSMENT OF THE ASSOCIATION BETWEEN PASSIVE SMOKING AND LUNG CANCER

A Dissertation

Presented to the Faculty of the Graduate School

of

Yale University

in Candidacy for the Degree of

Doctor of Philosophy

by

Luis R. Varela

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ABSTRACT

ASSESSMENT OF THE ASSOCIATION BETWEEN PASSIVE SMOKING

AND

LUNG CANCER

Luis R. Varela

Yale University

1987

A matched case-control study was carried out to evaluate the association between exposure to environmental tobacco smoke (passive smoking) and lung cancer risk. The study population was comprised of 439 cases of lung cancer diagnosed among non-smokers. All of these cases were clinically and histologically confirmed. The corresponding controls were drawn from the New York State Department of Motor Vehicles and were individually matched to the cases on age, sex, county of residence and previous smoking history. A face-to-face interview was applied to obtain information on exposure to environmental tobacco smoke. No increase in risk was found associated with exposure to three measurements of spouse smoking, or with exposure to co-workers' smoking. Conversely, exposure to the smoke of others in the household was found to effect the risk of lung cancer. For an exposure to 150 person/years of smoking the odds ratio was found to be 1.86. This effect seems to be larger for epidermoid and small cell tumors (OR=2.83) than for adenocarcinoma and other tumors (OR=1.42). Increasing exposure to passive smoking in social situations was found to be inversely associated with the risk of lung cancer. The implication of this finding -- at odds with previous results -- is discussed.

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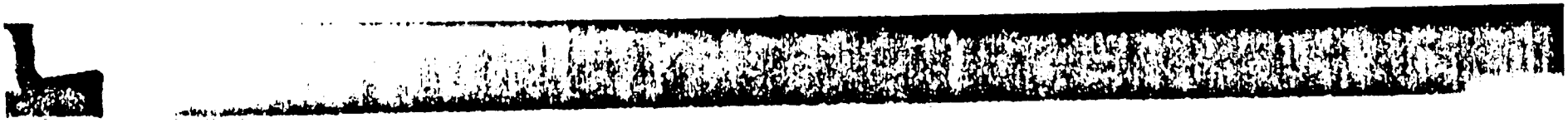

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CHAPTER ONE

LITERATURE REVIEW

1 BACKGROUND.

In 1972, the Report to the United States Congress on the Health Consequences of Smoking for the first time gave serious consideration to the issue of the effects of environmental tobacco smoke on the non-smoker (1). That others besides smokers themselves could experience detrimental health effects due to tobacco smoke had been in the minds of many for at least a decade. Obstetricians in particular seemed to have intensified this preoccupation, by reporting that cigarette smoking among pregnant women was associated with prematurity (2) and with low birth-weight (3). Other reports attributed a whole array of adverse effects of maternal smoking on the foetus, ranging from impaired post-natal development (4,5) to congenital malformations (6).

Later studies attended to the effects of tobacco components released into the environment at large. For instance, studies in the United States (7,8), England (9), Israel (10) and other countries (11) showed how children of smoking parents had higher incidence of

respiratory infections, as well as higher hospital admission rates. Laboratory investigations showed that exposure to maternal smoking produced a defective development of pulmonary function in children, as measured by forced expiratory volume in one second (12). Finally, reports of childhood tumors associated with parental smoking appeared in the medical literature, although often with contradictory results (13-17).

That there were serious health effects on the adult passive smoker — such effects as those experienced by the smokers themselves, i.e. lung cancer — was not considered possible as recently as a decade ago. This can be gathered from the following paragraphs published in 1975 :

> "In summary, the effects of cigarette smoke on healthy non-smokers consist mainly of minor eye and throat irritation. However, people with certain heart and lung diseases (angina pectoris, COPD, allergic asthma) may suffer exacerbation of their symptoms as a result of exposure to tobacco smoke-filled environments..." (18).

> " With respect to lung cancer there is no evidence to indicate whether or not this level of exposure has an effect on the risk of developing lung cancer. However, because of the low dosage and brief exposure, it would seem unlikely that there would be a significant increase in the risk of developing lung cancer " (19).

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It is an established fact that the overall cancer risk for non-smokers is lower than the cancer risk of the general population (20-22). Compared to smokers, non-smokers' risk for cancer is about 50% lower (20). For certain sites —in particular the respiratory tract— the differences are even more dramatic. A recent study, nonetheless, has suggested that lung cancer among non-smokers may be on the rise. The suggestion of such an increase among non-smokers has focused interest in passive smoking as one of its possible causes (23). This suggestion is partly based on a better understanding of the carcinogenic qualities of both mainstream and sidestream cigarette smoke, as will be discussed at a later point in this chapter.

Enstrom (23), using data from two representative samples of lung cancer deaths and mortality statistics at the national level, found for the period between 1914 and 1968 a 15-fold increase in lung cancer death rates among white nonsmoking males aged 35-84 years. The increase was the highest for those males over 65, estimated as 30-fold. For white females the increase has been 7-fold for the 35-84 age group. These changes seem so dramatic that the possibility of errors in Enstrom's estimates has been raised: some of his data sources go as far back as 1914, and there are no means by which to check their reliability. There are also reasons to doubt the accuracy of the ascertainment of smoking status in the surveys from which the data was obtained. Moreover, the categorization of the smoking variable changes from one source of data to another, as does the proportion of self-reported smoking versus surrogate reporting, thus making the use of pooled data difficult to interpret. It has also been

proposed that some of the changes described by Enstrom may be attributed to better diagnoses and/or changes in tumor classification. However, as the author has pointed out, the trend persists after 1935, when the major changes in diagnostic criteria had been implemented. Finally, there is the possibility — as Enstrom suggests — that the rising rates indicate the intervention of other factors in the causation of lung cancer in addition to personal cigarette smoking.

Other researchers do not agree with Enstrom's findings. Garfinkel (24) computed lung cancer mortality rates for non-smoking participants in two large prospective studies. In the American Cancer Society Study, 94,000 non-smoking males and 375,000 non-smoking females were enrolled between October 1959 and March 1960. The data used by Garfinkel spans the period between the end of the enrollment phase and June 30, 1972. The second study, the Dorn Study of Veterans, was initiated in 1954 with the mailing of questionnaires to 293,000 veterans. Fifty four thousands respondents reported themselves to be non-smokers. The follow-up period ended in 1969. Mortality rates for non-smokers in both of the groups studied were estimated, mainly through the use of death certificates. Rates were adjusted to the United States adult population of 1965. Garfinkel was unable to detect any increase in mortality due to lung cancer for three four-year periods between the years 1960-1972. Nevertheless, he reported a slight difference (although not statistically significant) in lung cancer risk for non-smoking women married to smokers, as compared to non-smoking women married to non-smokers. This was probably the first population study to consider such an association. The results will be discussed in the next section of this chapter.

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2 EPIDEMIOLOGIC STUDIES.

Controversial reports on lung cancer trends among non-smokers have not been discouraging enough to dismiss the hypothesis that passive smoking — also termed involuntary smoking or secondary smoking — is causally related to lung cancer. In January of 1981, the British Medical Journal published the first population study specifically addressing this issue (25). Hirayama reported the findings of a 14 year old prospective study which involved a follow-up for 91,540 non-smoking married Japanese women. One hundred and seventy four cases of lung cancer had developed in this group, for which the husband's smoking history had been collected independently. Women married to heavy smokers (>=20 cigarettes/day) showed a higher risk for lung cancer than women married to non-smokers (standardized risk ratio = 2.08). Furthermore, a statistically significant dose-response relationship was found: the relative risk for wives of ex-smokers or smokers of 1-19 cigarettes/day was 1.6; the relative risk for heavy smokers (>=20) was 2.08 (Mantel-extension X^2 test = 3.299; p, two tails = .00097. The trend was also observed when husbands' age and occupation was taken into account. The highest relative risk, 4.6, was found among women in agricultural families married to heavy smokers aged 40-59 years at time of enrollment into the study. No increase in risk for other major cancers was observed in relation to the husbands' smoking habits.

Hirayama's study received a great deal of attention among both the medical community and the lay public. His results and methods

were closely scrutinized, prompting an exchange of letters either critical or supportive of the study. The fact that the Mantel-extension test for one of the tables was calculated erroneously was particularly emphasized. A subsequent estimate obtained by rearranging the data was published subsequently (26). The new figure did not change the basic conclusion that the study factor and the disease were significantly associated. This reassurance, nonetheless, did not preclude criticism of the study on different grounds. First, the research work — started in 1966 — did not initially intend to look at the passive smoking-lung cancer association. This particular feature of the study might have affected the quality of the information in several opposite ways. On the one hand, it may be that the likelihood of bias in "reporting" or "interviewing" was less than if a well-developed hypothesis was being tested. This is because the study subjects, as well as the interviewers, were obviously blind to a hypothesis which was non-existent at the time of data collection. On the other hand, we should consider that the research, not initially intended to study the effects of passive smoking, may not have been as thorough in the ascertainment of exposure to passive smoking as would be necessary to detect a moderate or small effect. This latter point is not worrisome, however, since it would have resulted in a conservative estimate of the effect.

Secondly, in the original publication by Hirayama no details are given on the way in which deaths were ascertained, nor was there information available on the degree of pathological confirmation of the cancer cases. It is only through subsequent publications that we

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learn that in a subsample of 23 cases, 17 were adenocarcinomas. Since smoking has been postulated to be associated with specific histologic types this information would seem crucial.

Despite the drawbacks mentioned above, there are certain features about Hirayama's study that make it unique and probably very difficult to replicate. The prospective design involving a large population in more than one geographic region is certainly an asset. Also advantageous is the fact that the study was carried out in a traditional society where smoking habits of women are low, thus diminishing the probabilities of including erroneously classified women who developed cancer of the lung as a consequence of their own smoking. Also, in such a setting marriages may last longer, houses are certainly much smaller, and socializing for women usually takes place in the company of their husbands. All of the above suggests that quantification of the husbands' smoking habits may indeed be a good measure of exposure to secondhand smoke.

Also in 1981, Trichopoulos et. al. published the preliminary results of a study conducted in Greece (27). Using a case control design, they assembled a group of 40 non-smoking women diagnosed with lung cancer in three large Athens hospitals. The patients were interviewed regarding their husbands' smoking habits and were compared with the husbands' smoking habits of 149 non-smoking hospital controls. The controls were orthopedic patients who did not differ significantly from the cases with regard to age, education, duration of marriage, occupation or residency. The odds ratio for women married

to ex-smokers was 1.8; it was 2.4 if they were married to current smokers of 1-20 cigarettes/day; and 3.4 if married to current smokers of more than 20 cigarettes/day. This dose-response trend was found to be statistically significant (Chi-sq for linear trend = 6.45, p(2 tails) < .02.). When exposure to husbands' smoking over the course of the marriage was assessed a similar trend was observed. Estimated odds ratios were 2.5 for those exposed to 100 - 299 thousand cigarettes and 3.0 for those exposed to 300 thousand or more cigarettes (Chi-sq for linear trend = 6.56, p (2 tail) < .02).. This linear trend was identical in both group of cases: those with citological confirmation of tumor and those with clinical diagnosis only.

A later report of Trichopoulos' study in 1983 added nearly as many cases, and 50% more controls, to the study subjects (28). The results were substantially the same: odds ratio of 2.4 for wives of smokers of less than 20 cigarettes/day, and odds ratio of 3.4 for women married to smokers of more than 20 cigarettes per day (Chi-sq for linear trend = 6.7, p (2 tail) = .01).

The Greek study, although not entirely comparable to that of Hirayama, shows similar results. It also shares some of the advantages of the latter, namely, those concerning family structure and family social life, together with their implications on the assessment of exposure, as enumerated above. Different methodological problems, however, ought to be considered. For instance, the study group is small and the degree of pathological confirmation poor (only 65% had a citological or histological diagnosis). The study subjects (non-

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smoking women with lung cancer) represent about 78% of all the female lung cancer cases diagnosed in the participating hospitals. As is mentioned in a subsequent section of this chapter (see: Histologic Type and Lung Cancer) the proportion of non-smoking patients in other series of lung cancer cases has been established at about 10% for women. The excessively high proportion reported by Trichopoulos suggests that some of his cases may indeed have been smokers who did not admit to their tobacco habits for social or other reasons. Or, although the proposition is somewhat unlikely, it may be that non-smoking women with lung cancer in Greece are more likely to be hospitalized than in other parts of the world.

In addition, the fact that both cases and controls were interviewed by a single, unblinded researcher, points toward the possibility of misclassification of exposure. On the other hand, the attempt to assess exposure according to spouses' smoking habits during the total length of married life may have provided more complete ascertainment of exposure.

Pelayo Correa et. al., using a case-control design, assessed the risk of lung cancer for both non-smoking men and women with regard to the smoking habits of their spouses and parents (29). They found an odds ratio of 2.0 for 8 men married to women who smoked more than one pack of cigarettes a year. The corresponding odds ratio for 22 women married to smoking men was 2.07. Neither was statistically significant. After controlling for the spouses' smoking habit, maternal (but not paternal) smoking was associated with a higher risk

of lung cancer, as indicated by an odds ratio of 1.47 (Opposite results on this parental smoking-lung cancer association have been reported by Sandler, et. al.. Those results will be discussed latter in this chapter). The effect observed, however, was neither significant nor seemed to be dose-related. When exposure to both parents' smoking was combined, the odds ratio became significant only for those cases exposed to = > 41 packs of cigarettes per year (OR = 3.11, $\hat{p} < .05$).

Important drawbacks can be found in the study by Pelayo Correa et. al.. Its main disadvantage is the fact that the number of participants is so small that any of the possible strengths of the study -- such as the 100% histologic confirmation of diagnosis -- fail to compensate for this weakness.

A more recent epidemiologic study on the lung cancer-passive smoking relationship was carried out by Garfinkel, Auerbach and Joubert (30). Their group of cases was comprised of all female non-smoking lung cancer patients diagnosed in three hospitals in New Jersey and one hospital in Ohio. Women diagnosed with colon cancer served as controls. Three controls were matched to each case on the basis of age (+-5 years) and hospital of diagnosis. Pathology slides for both cases and controls were reviewed blindly in order to confirm the diagnosis. One hundred and thirty four lung cancer cases and 402 controls were then interviewed regarding the smoking habits of their husbands. Current smoking habits, number of cigarettes smoked at home, and number of years the husbands had smoked were assessed.

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Similarly, women were questioned about the number of hours a day they had been exposed to the smoke of others in the past 5 and 25 years.

It was found that women married to smokers of 40 or more cigarettes per day had an odds ratio of 1.99 (95% CL:1.13-3.50) as compared to those married to non-smokers. If half that amount of cigarettes was smoked at home, the odds ratio was estimated to be 2.11 (95%CL:1.13-3.95). Similarly, an increased risk was found for those women married to men who had smoked for 20-29 years (OR ~ 2.2), but, unexpectedly, not for those married to smokers of more than 30 years. No increase of risk was found to be dependent on the number of exposure-hours in the last five and 25 years.

Using logistic regression techniques, a model was fitted to the study data. The model included terms for possible confounders and several continuous variables representing exposure. An increase in risk with increasing exposure was found for the number of cigarettes smoked by the husband at home. This trend was statistically significant at the 0.05 level.

The study by Garfinkel et. al. attempted to tackle some of the methodological problems present in the former studies on passive smoking. The authors were successful in putting together a sizable group of cases who were confirmed never-smokers and whose diagnosis was histologically confirmed. Their assessment of exposure was not limited to the smoke derived from the husbands' smoking but included that experienced at the worksite and other areas. Powerful statistical techniques (logistic regression) were used to analyze the data, producing results consistent with the findings of the two other

major studies on this topic. It seems, therefore, that the only aspect of the study that could have affected the results is that which is most difficult to evaluate: the reliability of the data collected through the interview. Even though the interviewers were supposedly blind in regard to the hypothesis of the study and the case/control status of the participants, the participants themselves were aware of their own condition. In this situation the possibility of overreporting by the cases must be borne in mind. Additionally interviews of surrogate respondents may have affected the reliability of the information about the exposure variable. In fact, Marcel (31) has shown that Garfinkel's estimates of the odds ratios vary considerably according to the type of respondent. He found that the odds ratio for lung cancer was 3.57 (95% CL: 0.84-15.28) in the subgroup in which the respondents were either a daughter or a son of the study subjects. In the subgroup in which the husband provided information on the exposure he found that the odds ratio was 0.77 (95%CL: 0.56-1.06. And finally, in the subgroup of cases who reported about their own exposure, the odds ratio was estimated to be 0.83 (95% CL: 0.58-1.38).

At the same time that this report was being prepared, two additional epidemiologic studies claiming the existence of a moderate effect of passive smoking on lung cancer risks were published. The first of these was also conducted in Japan (32). It is a case- control study, but, as was true of its predecesor, it makes use of a cohort initially defined for another purpose (the study of the effects of atomic radiation in Hiroshima and Nagasaki survivors) in order to

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obtain its study subjects. The cohort, comprised of about 110,000 people, yielded 525 cases of lung cancer between 1971 and 1980. Pathologic diagnosis were done in 57% of these. Controls were selected from the same cohort among members who had not develop lung cancer. The controls were individually matched to the cases with regard to year of birth (+- 2 yrs), residence, sex, vital status, and whether or not they had belonged to the conort subgroup that underwent biennial medical examinations. Information was obtained for 428 cases and 957 controls. However, only 13 male cases and 94 female cases occurred among non-smokers. Among the non-smoking males the odds ratio associated with having a spouse who smoked was 1.8 (90% CL: 0.5 - 5.6). For females the corresponding figure was 1.5 (90% CL: 1.0 - 2.5). In addition, females showed an increase in risk of lung cancer with the increasing number of cigarettes smoked by the husband; the odds ratio being greater than 2.0 for the highest exposure category. The test of linear trend, however, was not statistically significant at the 0.05 level. Likewise, another measure of husbands' smoking -- the number of years the husband smoked -- was not statistically significant. Finally, their results showed that non-smoking women who had been exposed to the husbands' smoking in the last 10 years had a lower risk (OR = 1.3, 90% CL: 0.9 - 2.4) than those women exposed within the last 10 years (OR = 1.8, 90% CL: 1.0 - 3.2).

Some of the above estimates are consistent in their magnitude (if not in their statistical significance) with the results of the first Japanese study, as well as with the other studies on passive smoking. However, this subsequent study equally shares in some of the

methodologic problems that cast doubts over their results. One such problem is the poor rate of histologic confirmation. The authors, in trying to circumvent this problem, carried out separate analysis for those with pathologic diagnosis, as well as those without it. An undesired consequence of such approach, however, is the loss of statistical power due to the resulting smaller groups available for estimation of the parameters. Another potentially important problem concerns the obtaining of the information about exposure. Only 22 cases and 26 controls out of the total, although not necessarily out of the non-smoking group only, were available to be interviewed. Exposure for all others was assessed through the interviewing of surrogate respondents. Even though the distribution of types of surrogate respondents was similar for cases and controls, it cannot be ensured that selective recall was eliminated. A final point concerns the pecularities of the study group, survivors of the atomic explosions of Hiroshima and Nagasaki. Since both cases and controls were equal in that regard, we do not question the internal validity of the findings beyond the methodologic problems mentioned. However, we should be cautious in any attempt to extrapolate these results to the general population. It could be that the effect observed is only a product of a synergistic effect between radiation and exposure to tobacco smoke. This synergy, of course, would not be possible in the general population since on the whole it lacks exposure to the levels of radiation experienced by the subjects in this study. Finally, the authors of this study have been less than conservative in establishing that level of statistical significance which they are willing to accept. Values of p between 0.05 and 0.1 are reported as

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significant. Additionally, 90% confidence limits are reported instead of the conventional 95% CL. Although from a methodologic or statistical point of view there is nothing wrong with this approach, it raises concern that researchers, in order to detect and report "significant" effects, may take the risk of accepting a greater role of chance in their findings than that which is conventionally deemed appropriate.

The second most recently published article is based on the pooled data from three case-control studies (33). Ninety nine histologically confirmed lung cancer cases and 736 controls comprised the study group. These were all the participants in studies carried out in Louisiana, Texas and New Jersey who reported themselves to be never smokers. Due to the fact that the data came from three different sources, the type and level of detail of the information about passive smoking was not uniform for all study subjects. Nevertheless, information about exposure in the home environment was either available or could easily be estimated for everybody. Analysis of the data showed no increase in risk of lung cancer associated with ever having lived with a smoker (OR = 1.0, 95% CL: 0.64 - 1.56). Controlling in the analysis for the variables age, sex and study area, did not unveil any relationship either. The number of years lived with a smoker was not found to affect the risk of lung cancer. Conversely, some positive findings were described for exposure to the spouse's smoking. A smoking spouse was found to be associated with an odds ratio of 1.47 (not statistically significant). The number of cigarettes smoked a week by the spouse showed a linear relationship

with risk of lung cancer despite the fact that the estimates for each level of exposure, individually, did not reach statistical significance. The highest and only significant effect was reported for women 63 years or older married to blue collar workers who were heavy smokers (280 or more cigarettes/week).

3 OTHER STUDIES.

Despite the fact some studies were not intended specifically to look at the association between passive smoking and lung cancer (or at least this relationship was not the main focus of their inquiry), they provide information to contend that such connection is feasible. The study on lung cancer trends published by Garfinkel (24), as well as a study by Kabat and Wynder (34) on the histopathologic patterns of lung cancer in non-smokers, both fall into this category.

Similarly, studies linking passive smoking with cancers other than that of the lung can be helpful in delineating the carcinogenic potential of sidestream smoke. The studies by Sandler and colleagues (35-37) belong to this group.

Garfinkel (24) in his analysis of the American Cancer Society study compared the mortality rates for non-smoking women married to non-smokers with the mortality rate of non-smoking women married to smokers. It was found that women whose husbands smoked less than 20 cigarettes per day had a 27% higher lung cancer mortality rate than

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women married to non-smokers. The rate was only 10% higher for those married to a smoker of more than 20 cigarettes per day. When confounding variables were taken into account (age, race, education, residence and husbands' occupation), the excess risk was 37% and 4%, respectively. None of these findings were statistically significant. However, the results have to be interpreted with great caution because the study was never designed to obtain information on passive smoking. Furthermore, whatever smoking information was available corresponded only to the exposure at time of enrollment into the study.

Kabat and Wynder (34) assessed exposure to secondary smoke in a subset of non-smoking patients included in a large study of tobacco-related cancers. Out of 25 male cases six reported exposure to other people's smoke at home, as compared to 5 out of 25 controls. Eighteen of these cases reported exposure at work versus 11 of the controls. This last difference was barely statistically significant. Among the female group (n=53) about the same proportion of cases and controls were exposed to other people's smoke at home and work; consequently, the association with lung cancer was not statistically significant.

Sandler, et. al. reported the results of a case-control study involving 518 cancer patients (all sites, except basal-cell cancer of the skin) and 518 controls. In three separate publications the authors assessed the association between these cancers and: 1) exposure in childhood and adult life to the smoking of all household members who smoked (35), 2) early life exposure to parental smoking (36), and 3) exposure in adulthood as a result of spouse's smoking (37). In the first of these studies, the odds ratio for those exposed to one smoker

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in the household was found to be 1.5. If exposed to the smoke of two individuals, the odds ratio increased to 2.3, and to 2.8 if exposed to the smoke produced by three smokers. This trend was statistically significant ($p < 0.01$). However, it should be noted that an increase in risk was also observed for active smokers who had been exposed to the smoke of others in the household.

The overall cancer risk for all study subjects (passive, as well as active, smokers) was reported to be elevated in both of two circumstances: when exposure to secondary smoked had ocurred during childhood only (OR=1.6), and when the exposure took place in adult life exclusively (OR=1.5). For an individual exposed in both periods of life, the odds ratio exceeded two (OR=2.7).

For the second report, information on smoking habits of both parents was obtained for almost all the cases (n=438) and almost all of the controls (n=470). For all cancer sites the risk was increased for all the cases (again, passive and active smokers combined) if the father was a smoker (OR=1.5, 95%CL: 1.1-2.0). Maternal smoking, however, did not seem to increase the overall cancer risk (OR= 1.1, 95%CL: 0.7-1.6). Similarly, the risk for lung cancer was increased in those exposed to the father's smoke (OR=1.8, 95%CL: 0.5-6.6), but not to the mother's (OR=0.9, 95%CL: 0.4-2.1).

Lastly, when cancer risk was assessed in relation to the spouses' smoking habits, it was found that individuals married to smokers had 1.6 times the risk of individuals married to non-smokers ($p<0.01$). This difference could not be accounted for by differences in age,

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race, sex, education, or occupation between cases and controls. When site-specific cancer risk was assessed, the authors found that exposed individuals (those married to smokers) were at higher risk for cancer of the breast (OR=1.8), of the female genital organs (OR=1.8), and of the endocrine system (OR=3.2). Based on a small number of cases (n=22) it was found that passive smokers showed 1.9 times the risk for lung cancer than those not exposed to secondhand smoke. This finding did not reach statistical significance.

There are mainly three problematic features in Sandler's publications that deserve some attention. The first relates to the way in which the results have been presented. In many instances the risk for cancer associated with passive smoking is presented for the whole study group, comprising non-smokers as well as smokers. Although the latter group can be considered passive smokers of their own secondary smoke -- as well as of the smoke that others produce -- their inclusion seems inappropiate, since the overwhelming effects due to direct smoking would tend to distort the effect due exclusively to passive smoking. Some tables, however, do make the distinction between the two groups, and those are the ones that are most informative. Secondly, confounding variables that may explain the observed associations were not taken into account. Some of these variables are exposure to alcohol, to occupational hazards, to drugs, and to sexual and reproductive behavior variables. Thirdly and lastly, the fact that an association was found between passive smoking and cancers not previously described as tobacco-related (breast, endocrine system) raises some suspicion. This finding may be a

consequence of the inability to control for confounders, as mentioned above.

In addition to the epidemiologic studies, laboratory investigations, along with clinical and pathological observations, have supported the hypothesis that lung cancer and passive smoking indeed may be associated. The most relevant literature in these areas is discussed in the following paragraphs.

4 LABORATORY INVESTIGATIONS

Both observational and experimental laboratory studies have produced valuable information on the biological plausability of the health effects of passive smoking. The most important findings are related to the identification of carcinogenic substances in sidestream smoke and the ability of some sidestream smoke components to enter the organism of the passive smoker (38-45). Cigarette smoke contains over one thousand substances (46). Many of them, including carcinogens, are present in even higher concentrations in sidestream smoke than mainstream smoke. For instance, Dimethylnitrosamine, a potent carcinogen in animals, is 52 times more concentrated in sidestream smoke (47-48) Brunemann, et. al. (49) have estimated that a non-smoker who spends one hour in a smoky room may inhale nitrosamines in quantities equivalent to smoking about 15 cigarettes. Benzo(a)pirene, another known carcinogen in men and animals, is present 3.4 times as much in sidestream smoke. Furthermore, one cigarette may release up

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to 100 ng of that substance into the air (46).

But how much exposure to these substances does the regular non-smoking person really experience? This has been very difficult to quantify. The concentrations of tobacco components in the environment depends on numerous factors. The amount of tobacco consumed, the volume of ambient air, the size of the room where smoking takes place, and the type and amount of ventilation in an enclosed space are some of the many variables that affect smoke intake. The proximity of the passive smoker to the source of smoke and his/her pattern of inhalation may also affect actual exposure (48). Similarly, the smoking patterns of the individuals who do the smoking need to be considered. For instance, the variation in puff frequency, puff duration and puff volume are known to affect both the chemical composition of sidestream smoke and its biological activity (50-54). Even the smoker's health status seem to affect the way in which sidestream smoke is produced (55). In fact, it is the sidestream smoke that has been modified by the above and other factors that constitute the real exposure to the passive smoker. Some authors prefer to refer to this as environmental tobacco smoke rather than sidestream smoke.

Despite these difficulties, some studies have attempted to quantify actual exposure by measuring tobacco metabolites in body products. Serum thyocianate and cotinine are found in the blood, urine, serum and saliva of the passive smoker (45, 56-60). Although thyocianate may result from other sources — i.e. leafy vegetables —

cotinine is a specific marker for exposure to tobacco smoke and therefore its presence in the non-smokers is taken as evidence of passive inhalation. In one experiment a researcher was also able to identify mutagenic substances in the urine of subjects exposed to smoke in a poorly ventilated room (40).

Studies aimed at determining the specific deposition of environmental smoke components in the lung tissues are very scanty. In theory, the biological features of the anatomy and physiology of the human respiratory system, and the physical and chemical characteristics of sidestream smoke, suggest that such deposition takes place. The extent of it, however, has been a matter of debate. Different authors have reported high levels of smoke bronchial deposition ranging from 11% (61-62) to 80% (63).

Conversely, Repace and Lowry (64) think that most passive smokers are exposed to a minimal amount of smoke, perhaps no more than the equivalent of one cigarette per day. It has been suggested that such an exposure conveys a negligible risk (65). With respect to this, it should be noted that no treshold level of exposure for the development of lung cancer has been established. Therefore, any level of exposure — including the low level attained by passive smoking — should be considered potentially able to elicit a carcinogenic response.

Another series of studies have been aimed to detect the effects of passive smoking in the respiratory function of passive smokers. This is particularly relevant since some authors think that an

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impaired respiratory function is in itself a risk factor for lung cancer (66-69). In France, Kauffman (68) et. al. compared spirometric measurements between two types of non-smokers, exposed and non-exposed to secondary smoke. They found that both men and women married to smokers of >= 10 g of tobacco a day had a significantly lower forced mid-expiratory flow rate (FEF 25-75) than those married to non-smokers. In addition, women in the exposed group showed a decrease in forced expiratory volume in one second (FEV 1). The study carefully controlled for confounding variables such as age, social class, education, family size and air pollution.

White and Froeb (69) conducted a study in which the effects of passive smoking in the workplace were assessed. It was found that the decrease in forced mid-expiratory and end expiratory (FEF 25-75 and FEF 75-85) among passive smokers was comparable to the decrease observed in light smokers.

The effects of passive smoking on the pulmonary function of children as measured by spirometric measurements was mentioned in a preceeding section (12); they have been confirmed recently in a study by Chen and Li conducted in Shanghai (70).

Different carcinogenic mechanisms have been postulated for smoke both mainstream and environmental. These mechanisms are thought to explain the development of lung cancer among passive smokers even if, as some believe, the smoke dose conferred by passive smoking is low. Such mechanisms are also believed to be related to the different histologic patterns observed in smokers and non-smokers. According to

the first hypothesis, carcinogens present in environmental smoke would have the ability to produce adenocarcinoma, the type of cancer more common among non-smokers. Since volatile compounds are more likely to be absorbed by the passive smoker, it is precisely in those compounds where carcinogenic properties would reside. Furthermore, since volatile carcinogens would be able to reach the distal ends of the bronchial tree, one would expect to find more tumors in the periphery of the lungs of non-smoking cases than in smoking cases. Wynder and Goodman (67) suggest that, indeed, this anatomical preference is present among non-smokers.

The second (most widely accepted) hypothesis proposes that environmental tobacco smoke and mainstream smoke have exactly the same carcinogenic properties, despite the known differences in their physicochemical characteristics. Under this hypothesis, the exposure to environmental smoke is considered to be equivalent to low levels of exposure to mainstream smoke. The fact that no treshold has been established for the carcinogenic effect of maintream smoke (that is, that any level of exposure conveys a risk above that of no exposure) supports this hypothesis. Further support is provided by the observation that epidermoid and small cell carcinoma (considered by many to be the tumors more strongly related to active smoking) have been found associated with exposure to passive smoking (30,33).

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5 ANIMAL EXPERIMENTS.

Testing the hypothesis that passive smoking and lung cancer are related by means of animal experiments involves similar difficulties ascribed to the study of the carcinogenic effects of direct smoking. The search for a suitable animal model has taken many years, and while researchers are able to reproduce many of the respiratory system tumors, no one would claimed to have found an ideal model.

However, even without intending to do so, many of the experiments aimed at studing the effects of direct smoking may indeed have been testing the effects produced by passive smoking. Various species of laboratory animals (mice, rats, sytian hamsters) have been experimentally exposed to smoke-filled environments (72-75) One such study (72) now considered a classic in the field, has shown that rabbits exposed to environmental smoke may develop tracheobronchial epithelial metaplasia and dysplasia. This study, along with the others which followed it, were interpreted with much caution since they did not quite simulated the phenomenon they were intended to study (i.e. the effects of direct smoking). Different but equally important caveats should be taken into consideration when these studies are used to draw conclusions about exposure to passive smoking. For instance, we cannot be sure that exposure to smoke in a closed chamber actually simulates passive smoking, nor that the anatomy and physiology of the respiratory tract of the experimental animals would respond to secondary smoke in the same way as human's.

More recently, sophisticated equipment that produces and traps

sidestream smoke has been developed to simulate exposure to whole smoke or to its gas phase only (76). Such devices include exposure chambers for rodents, cell cultures or isolated perfused lungs, as well as mechanisms to manipulate smoke volume, dilution, and other variables to be studied. These devices are not yet part of the standard equipment of specialized laboratories, but it is likely that their introduction will produce a wealth of knowledge regarding the effects of sidestream smoke.

Lastly, many studies have presented evidence of the carcinogenic properties of tobacco components when administered through routes other than the respiratory tract. Many articles on the effects of subcutaneous injections of tobacco components (76-77), along with articles on the effects of rubbing and skin painting with tobacco compounds (76), agree that there is little reason to doubt the carcinogenic properties of tobacco smoke.

6 SMOKING AND HISTOLOGIC TYPE OF LUNG CANCER

An observation that has created a great deal of interest among researchers concerns differences found between lung cancer cases in smokers and lung cancer cases in nonsmokers. These differences pertain mainly to two factors, sex and histologic type. The relevant literature in this subject is discussed in the following paragraphs.

Among women with lung cancer there is a higher percentage of nonsmokers than among male cases. In upper New York State — as

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preliminary information for this study was being collected — we found that nonsmoking women comprised 9.0% of all female cases, whereas nonsmoking men represented only 2.0% of all male cases. Using data published by Greenberg et. al. (78), I estimated similar figures. In their series of cases, 10.7% of the women were nonsmokers versus 3.0% of the men. From data provided by Kabat and Wynder (34) the estimated corresponding figures are 14.9% and 1.96%. Finally, Garfinkel et. al. reported that 12% of the female lung cancer cases screened for participation in their study (30) were non-smokers.

It has been suggested -- since fewer women than men smoke — that a larger proportion of females are left susceptible to the effects of other carcinogens (including secondhand smoke) than to direct cigarette smoke. These carcinogens would be responsible for the "excess" number of nonsmoking female cases. The effects of these carcinogens in men would be masked by the overwhelming effect of direct cigarette smoke.

Histologic type has also been recognized to be associated with smoking habits. The nature of this association, however, remains controversial. As early as 1957, Doll et. al. (79) had proposed a "dose-response" relationship by showing an association between the amount of tobacco smoked and the development of epidermoid, large cell and small cell carcinoma. Other histologic types were found to be either unrelated, or only slightly related, to smoking. A few years later, Kreyberg published similar observations (80). He found an association between smoking and epidermoid, large cell and small cell

carcinomas. Similarly, he rejected an association between smoking and both adenocarcinoma and bronchioalveolar carcinoma.

From then on, no author has fully agreed with any other, presenting results that are often frankly contradictory. Weiss, et. al. (81) in a prospective study of 6,163 men, added adenocarcinoma to the list of histologic types related to smoking. Yesner (82) confirmed the association between smoking and small cell carcinoma, but not with other cell types. Auerbach found smoking habits to be equally distributed in all cell types, therefore denying any association between histology and tobacco smoke (83) Vincent concludes that adenocarcinoma and bronchioalveolar carcinoma are inversely related to smoking (84). And, more recently, two independent studies have reported that all cell types, including adenocarcinomas, are related to cigarette smoking (85).

The difficulties in interpreting the results of these studies are many. Two in particular, however, deserve to be mentioned. First, there is the problematic characteristics of the study groups. They comprise such heterogenous — and selected -- populations that possible sample bias is difficult to ignore. Secondly, the intervention of so many pathologists in the reviewing of the slides brings to mind the likelihood of unreliability of diagnoses. It should also be added that the studies cover an extended period, the mid fifties to 1984. During this period the ability to assign lung cancer cases to specific histologic types has changed, as can be assessed by the decreasing number of cases diagnosed as

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undifferentiated cell types.

A much clearer association is found between histologic type and sex. Most studies agree that epidermoid carcinoma is more frequent in males than females. The proportion of male cases classified as epidermoid carcinomas ranges between 38% and 64%. For females, the values are between 21% and 55%. The other notable difference occurs among adenocarcinomas: this tumor is much more common among women than men. Up to 52% of all lung cancer cases in females have been reported to belong to these group, whereas 33% is the highest among men to be presented in recent studies.

The difference in smoking habits between men and women suggests that such habits may be responsible for the difference in histologic types among the sexes. Unfortunately, this has not been properly assessed in any study. Most reports deal with the sex-histologic type, or the smoking-histologic type association. The three-way interaction, sex-smoking-histologic type, remains to be studied.

CHAPTER TWO

METHODS

In April of 1982 the New York State Department of Health initiated a large study of the epidemiology of lung cancer. New York State, with approximately 10,000 cases of lung cancer reported every year to its tumor registry, provided an excellent setting for a study of this nature. The project was intended to be comprehensive, that is, to include both smoking and non-smoking lung cancer cases. Study of the group of smoking cases was limited to the clinical and pathological characteristics of lung cancer, whereas the assessment of exposure to passive smoking and other relevant environmental variables were the main study variables in the non-smoking group. The study design also called for a population based case-matched control group (this group will be described later in full detail). It is only these two latter groups — non-smoking cases and their correspondent matched controls — that will be used to assess the effect of exposure to passive smoking on the risks of lung cancer. The

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methodologic approach used to this end is the one-to-one matched case control study.

It may be pertinent to mention that the original design of the study specified that, in order to discern more precisely the effects of passive smoking on the risk of developing lung cancer, all cases included would be never smokers. Two things were clear early on, however: first, that male cases were rarely never smokers (only 2.0% of those initially screened for inclusion in the study reported to have never smoked), and second, that a sufficient number of these cases could not possibly be assembled in a reasonable period of time so as to satisfy the sample size requirements. Therefore, the eligibility criteria for cases was extended to include those who had stopped smoking at least 10 years before diagnosis. It should then be clear that when we refer in this report to the group of non-smoking cases, we are referring not only to never smokers but also to former smokers. The implications of the decision to include former smokers in the study group are discussed in the later section of this Chapter that deals with methods of analysis, as well as in Chapter Four.

1 OBJECTIVES.

The main purpose of this study was to explore the relationship between passive smoking and lung cancer in non-smokers, using a case-control approach. This was done by analyzing data collected in 439

cases of lung cancer and 439 matched "healthy" population controls.

The specific question addressed in the analysis were:

1) Is there a risk for lung cancer associated with the spouses' smoking habits?

2) Is there a risk for lung cancer associated with smoking habits of members of the household (inclusive of spouse)?

3) Is exposure to passive smoking in the workplace associated with a higher risk of lung cancer?

4) Is passive smoking in social situations associated with a higher risk of lung cancer?

5) In the event that the answer to these questions is affirmative, does the association persist after controlling for confounding variables?

6) Can a dose-response between passive smoking and lung cancer be shown in this data?

7) Are there difference in risk for men and women?

8) Are there differences in risk for never smokers and for former smokers?

9) Is there a higher risk associated with a specific lung cancer histologic type?

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2 SAMPLE SIZE.

It was estimated that a sample size of 450 cases (225 males and 225 females), together with 450 controls, would be necessary to detect a relative risk of the order reported by Hirayama (25) and Trichopoulous, et. al. (27). Preliminary information collected in the study area showed that approximately 1,200 female lung cancer cases were diagnosed in the study area every year, and that 9.0% were among never smokers. Thus, it was estimated that (allowing for a 15% refusal rate) the 225 female cases could be assembled in a period of about 30 months, roughly the time available to collect the data for the study. Since only 2.0% of men were never smokers, gathering the same number of male cases would have taken much more time than the available period allowed. As indicated above, it was such a realization that prompted the decision to include cases that had stopped smoking at least 10 years back.

The final sample size fell slightly short of the proposed number. It was comprised of the 439 cases and their 439 matched controls, for which information was complete. Among all eligible cases the response rate was close to 80%. Subtracting an additional 4.0% for physicians' refusal to let their patients participate, the total response rate can be estimated to be 76%.

3 LOCATION OF THE STUDY.

A check of the data accumulated by the New York State Tumor Registry showed that about 80% of cases of lung cancer occur among residents of the eight Standard Metropolitan Statistical Areas of Upstate New York. This locale comprises 23 counties, with approximately 125 diagnostic and/or treatment facilities. It was decided that the resources available for the study would be used more efficiently — and the logistics of the field work greatly simplified — by limiting the study to that geographic area.

4 ESTABLISHMENT OF THE CASES REPORTING SYSTEM.

The first step of the project involved setting up a reporting system in all participating hospitals. The field staff, comprised of six experienced Research Assistants, was in charge of establishing the necessary contacts within the institutions. In each hospital the Medical Records Department, the Pathology Department, and the Tumor Registry reported to our field staff all clinically and histologically diagnosed lung cancer cases, either via telephone call or during the field staff regular visits to the hospital. Cooperation from all participating hospitals was excellent, with the largest facilities reporting as frequently as once or twice a week, and the smaller ones reporting at least once a month. The New York State Cancer Registry was also screened periodically to ascertain cases that might have been

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missed by the hospital-based reporting system. Special emphasis was put by the field staff on the timeliness of the reporting, since it was necessary for the purposes of the study to obtain personal interviews with the cases before they died or became too ill to participate. The mean time elapsed between diagnosis and reporting was estimated to be 45 days, with an additional 102 days transpired before the conducting of the interview.

The reporting of a case was followed by the securing of the smoking history stated in the patients' hospital medical records. All cases reported as never smokers, former smokers or of unknown smoking status were contacted by telephone and their smoking history confirmed. Only those confirmed never smokers, or ex-smokers for at least 10 years, were considerd for inclusion in the study. All the elegibility criteria for cases are listed below.

5 ELEGIBILITY CRITERIA FOR CASES.

1) The patient must be a resident of the 23 county study area (8 SMSA of Upstate New York).

2) The patient had to be between 20 and 80 years of age.

3) The patient had to be a never smoker (smoked <= 100 cigarettes in a lifetime) or an ex-smoker (smoked <= 100 cigarettes in the last 10 years).

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4) The patient should have a clinical or histological diagnosis of primary lung cancer made between July 1, 1982 and December 31, 1984.

5) The discharge diagnosis had to be confirmed by the re-examination of the pathology slides by an expert reviewer (see Histology Review in this Chapter).

Conversely, the exclusion criteria were as follows.

1) Any patient initially reported as a never or former smoker, who was later found not to comply with the definition of never and former smoker used in this study.

2) Any patient with a discharge diagnosis of primary lung cancer who, upon the re-examination of the histologic specimens, was assigned a different diagnosis.

3) Any patient not fulfilling the requirements of age, residency, or date of diagnosis.

4) Any patient for whom an individual or a physician's consent was not granted.

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6 SELECTION OF CONTROLS.

In order to provide a comparison group, each case was individually matched to a population control. The source for such controls was the State Department of Motor Vehicles files. This source was considered appropriate since it provided most of the information necesary to perform the matching. Additionally, this method was regarded as less time-consuming and more economical than other possible methods for the selecting of controls, such as random digit dialing. For each case, six potential controls were selected on the basis of age, sex, and county of residence. Upon a telephone interview, the first potential control who was found also to match the case on the basis of smoking status — and who, in addition, agreed to participate fully — was included in the study. In summary, the eligibility criteria for controls was as follows.

1) The control had to be of the same age (+ - 5 years) as the corresponding case.

2) The control had to be of the same sex as the case.

3) The control had to be a resident of the same county as the control.

4) The control had to have the same smoking history as the case. That is, both had to be either never smokers or ex-smokers for at least 10 years.

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An additional matching variable was considered at the time of conducting the interview. It concerns the matter of whether the questionnaire was responded to by the case himself/herself or, on the other hand, by a surrogate respondent. The matching on type of interview is better explained in the section of DATA COLLECTION which appears next on in this Chapter.

On the average, two potential controls had to be called until one matched the case on smoking history and was willing to participate in the study.

7 DATA COLLECTION.

Once the elegibility of cases and controls was determined, the field staff arranged a face to face interview which took approximately one hour to conduct in the patient's home. All information was collected using a pre-coded questionnaire. The questionnaire was pre-tested for a 3 month-period using patients diagnosed prior to the study period. The sections of the questionnaire that contain the items used for analysis in the present study are found in Appendix A. As would be expected, most of these questions are concerned with the measurement of exposure to passive smoking; but information on social, demographic and medical variables was also sought. Both cases and controls were interviewed exactly in the same fashion, and except for the items in the questionnaire referring to the clinical aspects of

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the current medical condition, they both answered the same number and type of questions.

When the field staff found that a case had died or had become too ill to participate, he/she would ask to conduct the interview with a next of kin, preferably with the spouse, but children and other relatives were also considered appropriate surrogate respondents. When a surrogate respondent had to be used for a case, a surrogate respondent was also used for the control. For instance, when the spouse of a case was interviewed in lieu of the case, we would seek to interview the spouse of the person selected as a control, even if the latter was available and willing to be interviewed. In this respect we should then note that cases and controls were matched in addition to SEX , AGE , SMOKING HISTORY and RESIDENCE, on the TYPE OF INTERVIEW conducted.

8 HISTOLOGY REVIEW.

An independent review of the pathology specimens initially examined to make the diagnosis of lung cancer seemed important for two reasons. First, to make sure that all cases were confirmed primary lung cancer cases, and second, to provide a uniform criteria of diagnosis. The procedure for such review was as follows.

The field staff would contact the pathology department of the

diagnosing hospitals and would request the slides or tissue blocks for the patient in question. In all but five patients such request was successful. The specimens would then be sent to a Pathologist at Memorial Sloane Kettering Cancer Center in New York City, who would review them blindly with regard to smoking history, the initial hospital diagnosis, and other risk factors. The review pathologist assigned each case a histological diagnosis according to the World Health Organization International Histological Classification of Tumours (86). The review diagnosis was then compared to the initial hospital diagnosis. If there was disagreement between initial and review diagnosis, a second pathologist from the same institution would review the slides and assign the final diagnosis. Even though a detailed histological classification was provided by the pathologists, for the purposes of these study we have used a coarse classification that divides our cases into the following histologic types: Epidermoid or squamous cell carcinoma, Small cell carcinoma, Adenocarcinoma, Large cell carcinoma, and Others.

9 EXPOSURE VARIABLES.

The main hypothesis of the study was concerned with the effects of passive smoking on lung cancer risk. In order to assess the magnitude of such an association, we needed to have both accurate measurements of exposure to the suspected risk factor and accurate measurement of the disease status. How the latter was achieved has

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been explained in the previous section dealing with histologic review. In this section it will be explained how the exposure to the risk factor was determined.

9.1 SPOUSE SMOKING HABITS.

Items 58 to 73 in the questionnaire (Appendix A) inquired about the smoking habits of up to four spouses per study subject. That information was used to create the following measurements of exposure: 1)Number of cigarettes smoked a day by the spouse(s). The number reported by the respondent was taken directly from the questionnaire if the case control had been married only once, or if only one of his/hers spouse(s) had smoked. If more than one marriage to a smoker was reported, the exposure was estimated to be the mean number of cigarettes/day smoked by as many spouses as reported (maximum 4). 2)Number of years the spouse smoked. This figure was taken directly from the reported number of years the first spouse smoked while married and living together with the study subject. When applicable -- that is, in the case of more than one marriage to a smoker -- the number of years smoked by subsequent spouses was simply added to the first figure. 3)Total number of cigarettes smoked by the spouse during married life. This variable was calculated by multypling the number of cigarettes smoked per day by 365 to obtain an estimate of the number of cigarettes smoked in a year; then, multiplying that figure by the number of years the spouse was reported to have smoked in the course of the marriage. When more than one spouse was reported as a smoker, the total married-life number of

cigarettes for each would be added into a single measurement of exposure.

9.2 EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD.

This variable was created with the information collected in the items marked with an asterisk in page 1/0 of Appendix A. Information about smoking in the household was collected for the 12 most recent residences in which the study subjects reported to have lived. It was calculated as follows: The number of years lived in each residence was multiplied by the number of smokers in that particular residence (inclusive of the spouse), and added over as many residences reported to have had smokers (maximum of 12). The resulting figure was expressed as the number of person/years of exposure experienced by the study subjects. It has to be emphasized that these units of exposure should not be confused with the conventional meaning usually attached to them in epidemiologic research. In this case these units are used to summarize the exposure of each individual according to intensity (number of smokers in the household) and duration (number of years living with smokers in the household) of such exposure. They do not indicate the collective experience of a group of individuals over a certain period of time.

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9.3 PASSIVE SMOKING IN THE WORKPLACE.

The information collected through the items marked with an asterisk in pages 168 and 169 of Appendix A was the basis on which to estimate exposure in the workplace. This variable was created in exactly the same manner as household exposure. That is, the number of years the study subject worked in a particular place was multiplied by the number of smokers who worked in the same room or area. This was done for the 12 most recent jobs and added over to obtain a single measurement of exposure. The units of exposure, as well as household exposure, are expressed in person/years; and their interpretation should also be similar: a summary of exposure for each study subject to smokers in the workplace over certain period of time.

9.4 PASSIVE SMOKING IN SOCIAL CIRCUMSTANCES.

Page No 173 in Appendix A shows the items asked during the interview in order to estimate exposure to secondary smoke in social circumstances. These items were intended to collect information on 3 aspects of exposure. The first is the type of social activities which are conducive to exposure to passive smoking; secondly, the frequency with which such activities were carried out; and thirdly, the stages in life (10 year intervals) in which such activities were carried out with that particular frequency. The information conveyed by these three aspects of exposure was summarized in a single index that goes

from zero to a maximum value of 96. This index is obtained by adding the information coded in items 186-200. For further details on the creation of the index of exposure the reader must refer to the Appendix. There, both the list of the activities included and the way in which the information was entered is self-explanatory.

10 POTENTIALLY CONFOUNDING VARIABLES.

Inspection of the data showed that cases and controls were different with regard to variables which were believed to affect lung cancer risk. It was decided that these should be considered in the analysis as potential confounders. We were aware, however, that the information available was not of uniform quality across variables. Whereas information on sociodemographic variables was likely to be highly reliable, the information pertaining to chemical and/or occupational exposures — all obtained on a self-reported basis — was not deemed so. Thus, we carried out the adjustment for confounding variables in two steps. The first, which we call "partial" adjustment, included only those variables for which we had "hard" information. Such variables were RELIGION (Catholic versus Other), INCOME, MARITAL STATUS (single versus other), and NUMBER OF CIGARETTES SMOKED/DAY among the former smokers. In the second step two other variables were added in order to carry out a "full" adjustment. These variables were: exposure to any of the CHEMICALS (never versus ever exposure) listed in items 202-218 in page 176 of Appendix A, and exposure to "FUMES, DUST OR RADIATION ON THE JOB" (see page 169 in

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Appendix A). In addition to these, other relevant variables were considered for inclusion, but a closer examination of their distribution among cases and controls showed no significant differences. These variables were: EXPOSURE TO DIESEL OR EXHAUST FUMES FROM BUSES, TRUCKS OR EQUIPMENT ; EXPOSURE TO A GAS COOKING RANGE AT HOME; EXPOSURE TO KEROSENE HEATERS; and EXPOSURE TO A COAL OR WOOD STOVE (pages 169 and 171 of Appendix A).

We believe that our best adjusted estimates were those obtained by the inclusion of the first group of variables, since they are based on the most reliable information. In the next chapter, therefore, we only present (in addition to the crude estimates) the results of the so-called "partial" adjustment.

11 ANALYSIS

The choice of statistical analysis techniques was primarily determined by the design of the study. The latter called for the use of techniques capable of accounting for the matching, as well as for techniques capable of dealing with complex situations in which covariates — in addition to the exposure variables — could be taken simultaneously into consideration.

Before explaining more fully how these techniques were applied, it is pertinent to mention that simpler techniques were also used to first explore the characteristics of the data collected. Univariate

statistics and/or simple frequencies were obtained for almost all of the variables for which we had information. Such exploration of the data also included — when apropriate — the use of stem and leaf or box-plot diagrams to determine the nature of the distribution of the variables, in both cases and controls. The comparability of these two groups also needed to be established and several statistical tests were performed to such an end. In the case of the variables that had been used to perform the matching (AGE, SEX, SMOKING HISTORY, RESIDENCE AND TYPE OF INTERVIEW), we knew of course that no differences were to be found. But there was no certainty that cases and controls would be equal in other respects. Sociodemographic variables such as number of years of school attendance, income, ethnic group, country of origin, number of times married, and others, were compared using either paired t-tests (continuous variables) or chi-square tests (McNemar's test for dicothomous variables or chi-square for categorical variables with more than two levels). In the same fashion those variables that were viewed as potential confounders were compared first before deciding whether or not to include them as confounders in the final analysis. When applicable, the comparison of the potentially confounding variables was done by treating the variables as both categorical (for example, yes/no exposure to gas cooking) and continuous (for example, number of years of exposure to gas cooking). Thus, the decision to include a variable as confounder was followed by the decision on whether to include it as a categorical or as a continuous variable. Logistic regression was used to determine if there was evidence to assume linearity on the effect of the potential confounder. It may be useful to advance now that none

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of the potentially confounding continuous variables (with the exception of income) showed indication of linearity. Therefore they were included only as categorical variables.

11.1 LOGISTIC REGRESSION FOR MATCHED CASE-CONTROL STUDIES.

Holford et. al. (87) have published a method to analyze pairwise matched studies based on the linear logistic model described by Cornfield et. al. (88). As pointed out by the authors, this method shows several features that make it the best available choice to analyze data sets such as the present one. First, it allows us to obtain the estimate of effect for one or more exposure variables while controlling for variables not considered in the matching. Second, it can provide estimates of the effect associated with different levels of one or more categorical exposure variables, as well as the estimates of effect for the levels (one unit change) of one or more continuous exposure variables. And third, it allows us easily to obtain estimates associated with the different levels of the matching variables.

In this adaptation of the logistic model the regressor variables are represented by the case-control differences of the value for the exposure (or confounding) variables, the intercept is not included, and the response is always positive (that is, for each value of the regressor variable there is always one case and one control). The resulting estimates are the maximum conditional likelihood estimates

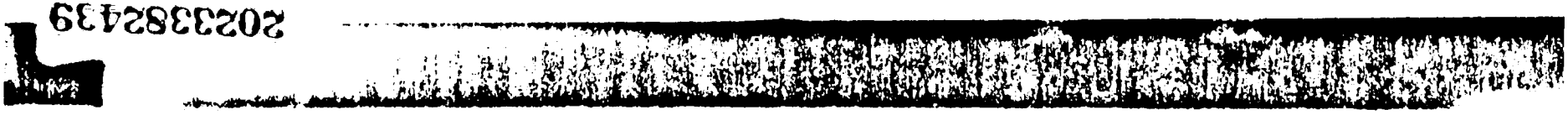
of the parameters.

In the present analysis I used the program for logistic regression available in GLIM (89). The analysis of each of the exposure variables proceeded very much in the same way. The following, therefore, is a general description of the steps followed to assess the effect of each of these exposure variables on the risk of lung cancer.

11.2 EXPOSURE AS CATEGORICAL VARIABLES.

All information on exposure was collected in such a way as to allow the creation of variables that would reflect such exposure in a continuous scale. We considered it useful, however, to look first at the effect of the exposure variables as ordinal categories. For that matter all variables were transformed into new categorical variables. The cut-off points for the categories were chosen by following convention (e.g. packs of cigarettes/day) or by referring to what other authors have used in their studies (e.g. Trichopoulous categorization of exposure to cigarettes in a lifetime). Once the categories had been created and the information summarized in tables, the analysis proceeded in this way:

1) The model that assumes no association between risk factor and disease was fitted to the data. This is also referred to as the model with no parameters or the model of total symmetry.



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2) The logistic model that considers exposure as an ordinal categorical variable was fitted to the data. These models provided estimates of the effect of each of the levels of exposure using zero exposure as the reference category.

3) In order to test for a linear trend in the levels of the category, a third model was fitted. This included as the regressor variable the case-control differences of the mid-points of the category intervals. The estimate obtained represents the slope of the fitted line.

4) In order to test for the significance of the overall effect of the exposure variable, the model obtained in 2 was compared to the model obtained in 1. The resulting difference in G^2 tests the null hypotheses that all parameters in model 2 are zero, or equivalently, it tests whether model.2 provides a better fit to the data than the model of no association.

5) In order to test for the significance of the linear trend, model 3 was compared to model 1.

6) The statistical significance of the parameter estimates obtained in 2 and 3 was assessed by comparing each estimate to its standard error (Wald's tests not shown), or by estimating their 95% confidence intervals.

7) Violation of the assumption of the consistency of the odds ratios was checked by looking at the value of G^2 obtained in model 2 (Test of Quasy symmetry). The assumption of the consistency of the odds ratios is made under the adaptation of the logistic model used for the analysis of matched studies.

8) In the one case that the linear trend was found to be significant (exposure to passive smoking in the household), the next higher order model was fitted to the data. The quadratic term was represented by the case-control differences of the squares of the mid-points of the category intervals.

9) A last regressor variable was entered to compare the risk associated with zero exposure to the risk associated with any level of exposure (none versus some exposure). None of these models showed any significance and since they provide only a "coarse" assessment of exposure, they are not presented in the results.

11.3 EXPOSURE AS A CONTINUOUS VARIABLE.

The next step in the analysis was to treat the exposure variables as a continuum. It was believed that such an approach could detect significant effects not uncovered by the analysis of the exposure as

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categories. At this point it was also considered pertinent to look at estimates for specific strata of the study population. Previous studies have suggested that the effect of passive smoking may vary between the sexes, or by type of interview or according to smoking history. The matched design would not allow us to obtain estimates for the main effects of such variables (by design those effects have been set to be zero), but estimates for each of their levels could provide useful information on the relationship between the risk factor and the study disease. Also, previous research work has suggested that passive smoking may determine the type of histologic tumor developed by the patients. Therefore, we wanted to see if the magnitude or direction of the effect varied according to the histologic type considered.

In summary, the steps taken at this stage of the analysis were as follows.

1) A logistic model was fitted for each of the exposure variables. These models provided estimates of effect for the exposure in question, taking into account all 439 pairs available for analysis.

2) A logistic model was fitted for each of the exposure variables and their interaction with the variable TYPE OF INTERVIEW. From these models estimates for effects were obtained for SELF-RESPONDENTS and for SURROGATE RESPONDENTS.

3) A logistic model was fitted for each of the exposure variables and their interaction with the variable SMOKING HISTORY. From these models separate estimates were obtained for NEVER SMOKERS and FORMER SMOKERS.

4) A logistic model was fitted for each of the exposure variables and their interactions with the variable SEX. These models provided estimates for FEMALES and MALES.

5) A logistic model was fitted for each of the exposure variables and their interactions with the variable HISTOLOGIC TYPE. Separate effects were obtained for EPIDERMOID AND SMALL CELL CARCINOMA and ADENOCARCINOMA AND OTHERS.

6) Tests of the significance of the effects of all of the above parameters were obtained, as well as tests of the significance of the interactions. The latter are equivalent to testing the null hypothesis that the effect does not vary according to the levels of the stratifying variable.

7) More complex models including the exposure variable in question and two, three and four two-way interactions were fitted.

8) Models with the exposure variables and all the possible combinations of three-way interactions were fitted.

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9) Models obtained in 8 and 9 were compared to each other as well as to the simplest models obtained in 1 through 5.

10) The variables selected as potential confounders were included in the models obtained in 1 through 5.

11) A single model that contained the three mutually exclusive exposure variables (household, workplace and social exposure) and the confounders was fitted to the data.

12) A model was fitted to the data that contained only the two variables with significant effects and the confounders.

CHAPTER THREE

RESULTS

This chapter is divided into three sections. The first is devoted to the description of the study sample in terms of socio-demographic characteristics. In addition, it checks the distribution of the variables used to match cases to controls and presents the distribution of cases regarding histologic diagnoses. The second section examines the distribution of certain variables not taken into account by the matching process — variables which, by their nature, may be considered as potential confounders of the association between passive smoking and lung cancer (for example, pipe and cigar smoking). The third and last section is subdivided into four subsections, each one reporting the assessment of the association between lung cancer and a different measurement of exposure to passive smoking.

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1 DESCRIPTION OF THE STUDY SAMPLE AND DISTRIBUTION OF THE MATCHING VARIABLES.

The results presented here are based on the statistical analysis performed on data pertaining to 439 case-control pairs. Table No 1 presents the most relevant demographic characteristics of the study subjects. By design (i.e. matching), the sex distribution was set to be approximately even. Thus, there are 218 (49.7%) female case-control pairs and 221 (50.3%) pairs of males. In the same manner, age, which was matched within a + - five year age range, caused the mean age for the cases (67.05 years) to be very close to the mean age for controls (68.13 years). As is well known, most lung cancer patients acquire the disease later in life. This is likely to be a reflection either of a long latency period or of the requirement of a prolonged exposure to etiologic factors necessary for the development of the disease). Moreover, 77% of our case control-pairs reported themselves 60 years or older at the time of diagnosis. By the time the interview was conducted, an additional 3.0 % were reported to fall into that category. The latter increase was obviously due to the time elapsed between the discharge diagnosis, the obtaining of consent from the attending physician, the contacting of the patient him- or herself and, finally, the arrangement and conducting of the interview. Since survival among lung cancer cases is known to be poor, and since obtaining the information directly from the patient before death was considered crucial for the quality of the data sought, we tried to keep the lapse between diagnosis and interview as short as possible. As a consequence, the mean number of days that transpired between the

two events was 147 days. This allowed us to conduct direct interviews with 296 of the patients (67.0% of the total). As explained in the preceding section, cases and controls were also matched on type of interview, so that the same proportion of direct interviews applies to the control group.

One hundred and ninety seven pairs (45%) were comprised by never smokers and 242 (55%) by former smokers. As would be expected, most never smoking pairs were female (75.6%) and most smoking pairs were male (71.5%). The smoking history-sex distribution will be important when interpreting the results of the exposure variables. It must be remembered, therefore, that when presenting results for females we will be dealing mostly with non-smokers, and when presenting results for males we will be referring to a subgroup composed mainly of former smokers. Conversely, estimates for never smokers are based on more females than males, and estimates for former smokers on more males. In evaluating interactions we must also keep in mind that the estimates of effect for specific subgroups will be based on a varying number of pairs, and therefore will have different statistical power, depending on the particular interactions being evaluated. Thus, for instance, the estimates for never smoking males, will be calculated using smaller number of subjects than the estimate for former smoking males.

Over 90% of both cases and controls were whites. Blacks constituted 3.6% of the cases and 2.7% of the controls. No information on ethnic group was available in about 1% of cases and

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controls. Most patients reported themselves as having been born in the United States (88%). In addition to this country, 22 other countries, mostly European, were mentioned as place of birth. None of the differences in the distribution of ethnic group or national origin were statistically significant.

Fewer cases than controls reported ever to having been married (87% versus 92%). Similarly, at the time of the interview, fewer cases (60%) were reported to be married than controls. While these differences were statistically significant (Chi-square = 11.46, 1 df) the number of times being married or the mean number of years duration of marriage were not. Significant differences of religion were offered by the presence of more Catholics (54%) among the cases than among the controls (42.0 %), and by more Protestants among the controls (38%) than among the cases (32%) (Chi-square = 13.67, 4 df). Income was found to be significantly higher for the cases than for the controls. This finding suggests that matching on county of residence does not seem effective to control for economic status. However, another variable which is generally considered to be an indicator of socioeconomic status, i.e. number of years of school attendance, did not show any significant differences for cases and controls. The mean number of years of school attendance for cases was 11.44 years and, for controls, 12.7 years.

The distribution of histologic diagnoses resulting from the study review indicates that the majority of cases in our study were adenocarcinomas (222 cases, 50.6%); epidermoid carcinoma constituted

TABLE No. 1
RELEVANT CHARACTERISTICS OF THE STUDY POPULATION

	CASES	CONTROLS
SEX*		
FEMALES	49.7%	49.7%
MALES	50.3%	50.3
AGE*		
MEAN AGE IN YEARS	67.05	68.13
SMOKING HISTORY*		
NEVER SMOKERS	45.0%	45.0%
FORMER SMOKERS	55.0%	55.0%
TYPE OF INTERVIEW*		
SELF-RESPONDENTS	67.0%	67.0%
SURROGATE RESPONDENTS	33.0%	33.0%
ETHNIC GROUP		
NON-WHITE	2.7%	3.6%
WHITE	86.6%	85.6%
EDUCATION		
MEAN NUMBER OF YEARS OF SCHOOL ATTENDANCE	11.4	12.7
PLACE OF BIRTH		
UNITED STATES	89.7%	86.8%
OTHER	10.3%	13.2%
RELIGION		
CATHOLIC	54.0%	42.4%
OTHER OR NONE	46.0%	57.6%
HISTOLOGIC TYPE		
EPIDERMOID	50.6%	-
ADENOCARCINOMA	25.1%	-
LARGE CELL	10.3%	-
SMALL CELL	7.7%	-
OTHER	6.4%	-

* Matching variables

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about one quarter of the patients (110 cases, 25.1%); large and small cell accounted for 45 (10.3%) and 34 (7.7%) cases. Finally, 28 patients were classified as "other" histologic types. We want to emphasize that this categorization of cases according to histologic diagnoses is based on the diagnoses provided by our study review, (except for the five cases in which the pathology slides could not be obtained). This distribution is very similar to the one derived from the initial hospital diagnoses. The overall agreement between the latter and our study review was 94.0%, with a Kappa value of 0.864.

2 DISTRIBUTION OF POTENTIALLY CONFOUNDING VARIABLES.

Some of the socio-demographic variables already described fall into the category of potentially confounding variables. Namely, marital status, income and religious affiliation. The magnitude and nature of the differences between cases and controls regarding these attributes have been pointed out, and the ways in which they have been taken into account in the analysis has been presented in the previous chapter. Other potentially confounding variables such as chemical, occupational, and residential exposures have been discussed in section 10 of the same chapter. Therefore, this section will concentrate on the non-matching variables not yet discussed. Of particular importance are those variables related to smoking habits. As explained in the previous section, the matching on smoking history was done on a dicothomous basis. That is, cases who were never smokers were matched to controls who never smoked, and cases who reported as having smoked

were matched with controls who were former smokers. This procedure, however, did not necessarily ensure that the particularities of the smoking habits of the former smokers -- such as intensity and duration of cigarette smoking -- were comparable among cases and controls. Nor did this procedure ensure that exposure to other forms of tobacco was similar in both groups. Thus, the exploration of the distribution of these variables seems in order.

The average number of years the ex-smoking cases reported having smoked was 29.9 years. This figure was not significantly different from the mean 28.3 years duration of the smoking habit reported by controls (paired t-test = 1.64 , p=.1024). However, the mean number of cigarettes per day smoked by the ex-smoking cases (28.9) was significantly higher than the mean daily number of cigarettes smoked by the controls (23.82) (paired t-test=3.74, p= .0002). This finding was recognized to be important for two reasons. First, it suggested that if an increased risk for lung cancer was found in the study, it might be due to the residual effect of past smoking habits, and not -- or not only -- due to exposure to passive smoking. Secondly, it made clear the need to control for this variable in the final analysis as a way to remove the potentially confounding effect, as well as to stress the need to obtain separate estimates of the effect of passive smoking for never and former smokers.

Exposure to other forms of tobacco did not show any significant difference between cases and controls. Both groups had about the same proportion of individuals who reported ever smoking cigars (78 cases

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and 79 controls). The intensity of this habit was also similar for cases and controls (4.6 cigars/day for cases and 3.4 cigars /day for controls), as was the overall length of use (20.5 years for cases and 18.26 years for the controls). Cases and controls were also similar in proportion, intensity, and duration of pipe smoking. Eigthy three cases and 90 controls were ever pipe smokers. The cases smoked and average of 4.4 pipes a day during an average of 20.41 years. The controls smoked 4.6 pipes a day during an average of 19.9 years. The appropiate statistical test did not show significant differences for any of these variables. Only 3 cases and 1 control reported having smoked marijuana. This difference is not significant, and in any case the comparison is based on such small numbers as to have no meaningful interpretation or to raise concern regarding any effect on the results.

3 ASSESSMENT OF THE EFFECTS OF PASSIVE SMOKING ON LUNG CANCER RISKS.

In the following section the results of assessing the impact of passive smoking on lung cancer risk will be presented according to four different sources of exposure. These sources are: 1) smoking habits of the spouse(s), 2)smoking by all members of the household (inclusive of spouse), 3) smoking in the workplace, and 4) smoking that occurs in social circumstances.

3.1 SMOKING HABITS OF THE SPOUSE.

Most epidemiologic studies have chosen one measurement of spouse smoking as an indicator of exposure to passive smoking. In the present study the effect of spouse smoking as measured by three variables has been evaluated. The first variable considers the daily smoking habits of the spouse(s). The second concerns the number of years the spouse(s) sustained that particular smoking pattern. And the third variable — in fact a combination of the first two — reflects the total number of cigarettes smoked by the spouse(s) while married and living together.

3.1.1 ASSESSMENT OF THE EFFECT OF NUMBER OF CIGARETTES/DAY SMOKED BY THE SPOUSE.

Table No 2 presents the estimates of the effect of the spouse's daily smoking habits when analyzed as an ordinal categorical variable. In order to present results easily compared with those of other studies, each category reflects the standard number of cigarettes corresponding to a different number of packs of cigarettes/day. A logistic regression model was fitted to the data using the differences in exposure between cases and controls as regressor variables (See Statistical Analysis in the Methods Chapter). Through this technique, comparisons have been made between the risk associated with exposure to each of the categories of spouse daily smoking and the referent category represented by zero exposure. Table

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No 2 presents the estimates, standard errors, odds ratios and confidence limits for each of these comparisons. The highest risks observed correspond to odds ratios of 2.86 (for exposure to spouse smoking of more than 80 cig/day) and 1.23 (for exposure corresponding to 41 to 60 cigarettes/day). The corresponding confidence limits, however, indicate that these values are not significantly different from the null value. Unexpectedly, three of the estimates in the table suggest a decrease in risk for lung cancer for those exposed to 1-20 cigarettes/day (OR=.7897), to 21-40 cigarettes/day (OR=.9063), and to 60 to 80 cigarettes/day (OR=.4196). Likewise, these estimates are not statistically different from the null value, as shown in the same table.

A plot of the five log odds corresponding to each category is shown in Figure No 1 (estimates represented by diamonds at midpoint of category values). Four of the points suggest a possible linear relationship. In order to test for linearity in the categories, the case-control differences of the mid-points of each category were entered as the regressor variables in the logistic model. The estimate obtained for the slope of the fitted line (estimate=.001032, Wald test=.2271) was not statistically different from zero, therefore concluding that there is no evidence to support a linear response for the categories.

When compared to a model of total symmetry (G^2 = 10.29, 11 df) — that is, to a model with no parameters, that assumes no differences in exposure for cases and controls — neither the model for exposure as categories (G^2 = 5.304, 6 df), nor the model for linear trend (G^2 = 10.24, 10 df), seemed to provide a better fit to the data (ΔG^2 = 4.99, 5 df, and ΔG^2 = .05, 1 df, respectively). Along the same lines, a logistic model that compares zero exposure to any exposure (=> 1 cig/day) showed neither any significant effect nor any appropiate fit to the data, when compared to the model with no parameters (ΔG^2 = 2.72, 2 df).

The analysis of the effect of number of cigarettes/ day smoked by the spouse also included treating the exposure as a continuum. For that purpose a linear logistic model was fitted to the data. The odds ratio associated with the spouse smoking 1 pack of cigarettes/ day was 1.011 (Table No. 3. Its 95% confidence limits (0.866 - 1.18) includes the null value and therefore provides no evidence of a significant association with the study disease. It may be pertinent to mention at this point that when logistic regression is applied to the analysis of continuous data, the estimate of effect obtained for a particular unit of exposure can be used to calculate the estimate associated with other levels of exposure. For instance, by multypling the estimate for 1 pack of cigarettes/day (0.010998) by 2, 3 or 4, we would obtain the estimates of effect associated with the spouse smoking the respective number of packs/day. In the same fashion, multiplying the standard error of 1 pack/day by the quantities cited above will yield the variation associated with the estimate at that level of exposure. It should be evident by the way in which these estimates are obtained that higher exposures will always be associated with larger estimates (as well as with greater variation) so that the statistical significance of the estimates does not vary according to

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level of exposure. In the present case, the estimates for 2, 3, and 4 packs cigarettes/day would all be not significantly different from the null value; their confidence intervals would include such a figure.

Figure No 1 shows the line that represents the relationship between exposure (cigarettes/day in the X axis) and risk of disease (log odds in the Y axis), according to the logistic model fitted to the data (continuous line). Again, the almost entirely flat line suggests a lack of dose response relationship. The two other lines represent two subgroups of the study population. The large dash line corresponds to self respondents, and the small dash line to surrogate respondents. Both of these lines would seem to suggest effects due to exposure that are not only greater than the effect for the group as a whole, but also that move in opposite directions from one another. However, neither is significantly different from the line that represents all subjects, nor are they significantly different from one another. Likewise, the estimates that describe these lines are not significantly different from the null value.

The lower part of Table No 3 (lines 4-9) and Figures No 2, 3, and 4, present for the study population estimates and fitted lines, respectively, according to SMOKING HISTORY, SEX and HISTOLOGIC DIAGNOSIS. The significance tests and confidence limits in the table show no significant effect of spouse daily smoking when examined separately for never smokers and former smokers, males and females, and epidermoid and adenocarcinoma histologic types. Moreover, the tests of interaction of the exposure variable with SMOKING HISTORY,

TABLE No. 2

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO FIVE CATEGORIES OF CIGARETTES PER DAY SMOKED BY THE SPOUSE(S).

CIGARETTES /DAY	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 20	-.2361	.1558	.7897	.6819	1.0717
21 - 40	-.0984	.2032	.9063	.6086	1.3497
41 - 60	.2081.	.3390	1.2313	.6336	2.3930
61 -80	-.8684	.8751	.4196	.0755	2.3322
80 +	1.0500	1.1590	2.8576	.2947	27.7058

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

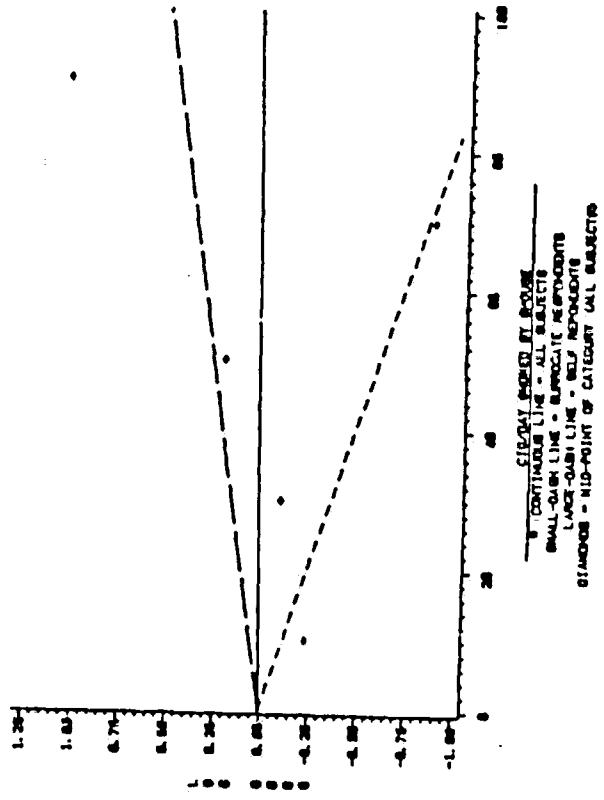
TABLE No 3

UNADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO
SPOUSE SMOKING OF 20 CIGARETTES/DAY.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.010998	.07928	1.0111	.8655	1.1810
SELF RESPONDENTS	.1072	.0940	1.1132	.9258	1.3384
SURROGATE RESPONDENTS	-.2402	.1543	.7865	.5812	1.0642
NEVER SMOKERS	-.0614	.1302	.9499	.7359	1.2262
FORMER SMOKERS	.0656	.1040	1.0571	.8622	1.2962
FEMALES	-.0230	.1059	.9773	.7941	1.2028
MALES	.05444	.1200	1.0560	.8347	1.3358
EPIDERMOID SMALL CELL	.1157	.1378	1.1227	.8570	1.4707
ADENOCA. & OTHERS	-.0420	.0980	.9589	.7913	1.1619

FIGURE No. 1

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No. 2

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

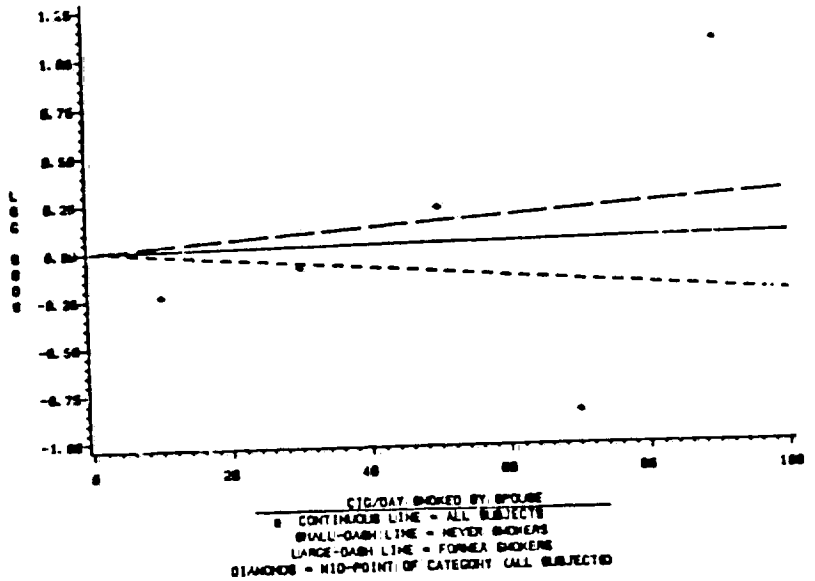
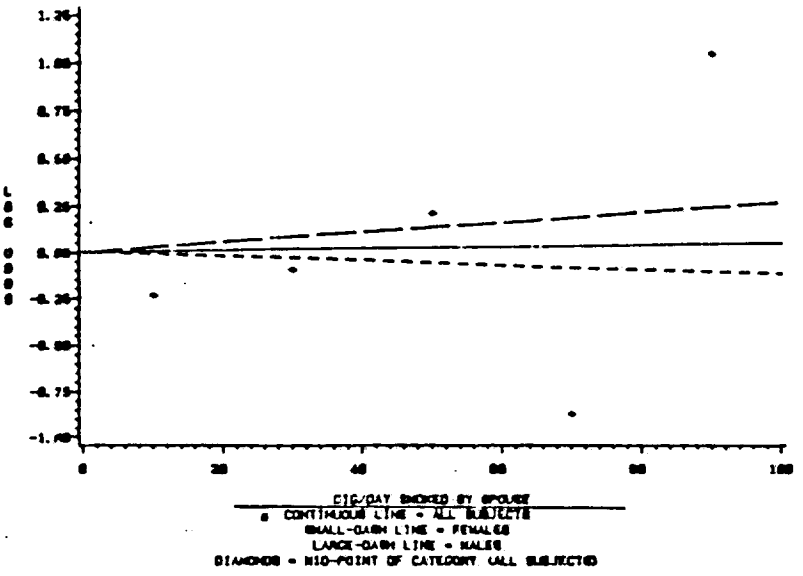


FIGURE No. 3

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

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FIGURE No. 4

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES

AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

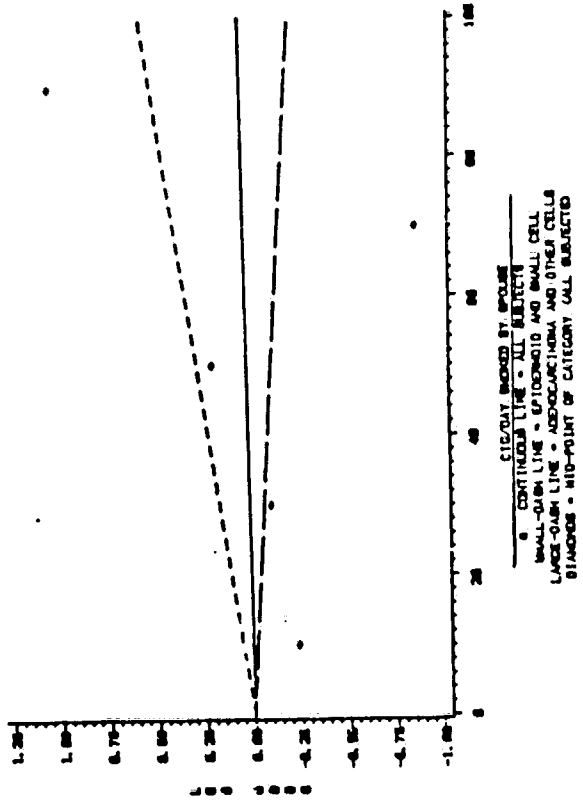

TABLE No. 4

ADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 20 CIGARETTES/DAY.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0152	.0831	.9849	.8369	1.1591
SELF RESPONDENTS	.0838	.0987	1.0874	.8962	1.3196
SURROGATE RESPONDENTS	-.2684	.1588	.7646	.5601	1.0437
NEVER SMOKERS	-.0684	.1271	.9338	.7279	1.1981
FORMER SMOKERS	.0247	.1101	1.02501	.8261	1.2718
FEMALES	-.0597	.1107	.9421	.7583	1.1703
MALES	.0454	.1274	1.0444	.8136	1.3407
EPIDERMOID/ SMALL CELL	-.0813	.1837	.9219	.6431	1.3215
ADENOCA. & OTHERS	-.0491	.1181	.9521	.7554	1.2001

Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

SEX, AND HISTOLOGIC DIAGNOSIS are not significant, indicating that the estimates for the two subgroups in each of these stratifying variables are not significantly different from one another.

Table No 4 presents estimates for ALL SUBJECTS and for each level of the variables TYPE OF INTERVIEW, SMOKING HISTORY, SEX and HISTOLOGIC DIAGNOSIS obtained with the logistic regression model that includes confounding variables. A comparison of these values with those presented in Table No 3 shows no meaningful differences. The tests of significance support the previous conclusion of no significant association between exposure and study disease. There is also no evidence of differences in the lines representing the different subgroups for which the effect of exposure is being evaluated.

3.1.2 NUMBER OF YEARS OF SPOUSE SMOKING.

The assessment of years of exposure to spouse smoking as an ordinal categorical variable did not show evidence of a significant association with the study disease (Table No 5) All of the six estimates are accompanied by test results that are not statistically significant, as well as by confidence limits that include the null value. A plot of the estimates in Figure No. 5 (diamonds in mid-point of categories) did not suggest a strong dose-response relationship either. The absence of such relationship was confirmed by a non-significant test for the regressor variable representing a linear trend for the categories (estimate= -.00193, Wald= -.4552).

When number of years of spouse smoking was assessed as a continuous variable (Table No.6) it was found that 10 years of spouse smoking was associated with an odds ratio of 0.99 (95% CL: 0.912 - 1.074). Exposure to as much as 50 years of spouse smoking, roughly the highest exposure observed in these data, would decrease the odds ratio to 0.95 (95% CL: .6200 - 1.4600); but again, this is not statistically different than the risk for the non-exposed. Also in Table No 6 and in Figures No. 6 - 8, the estimates and fitted lines for the different levels of the matching variables and the two histologic types are presented. As shown, the point estimates for each of these subgroups fluctuates between positive and negative values, which in no case present evidence of being significantly different from the null value. Likewise, the estimates are not significantly different between levels of the variables SEX, SMOKING HISTORY and HISTOLOGIC DIAGNOSES, as evaluated by the interaction with the exposure variable. However, the interaction between the latter and TYPE OF INTERVIEW was found to be significant (Wald test= 2.13 > 1.96, $p < .05$), suggesting that the estimate for surrogate respondents is different from that for self-respondents. Nevertheless, as mentioned above, neither can be considered to be significant.

The inclusion of confounding variables in the logistic model generated the estimates presented in Table No 7. An inspection of these figures, for all subjects and by levels of the stratifying variables, supports the conclusion conveyed by the unadjusted estimates that there is no association with the study disease. Although this basic conclusion is not changed, it should be noted that

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TABLE No. 5

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO SIX CATEGORIES OF NUMBER OF YEARS SMOKED BY THE SPOUSE(S).

NUMBER OF YEARS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 10	-.0970	.2252	.9076	.5837	1.4112
11 - 20	-.3879	.2595	.6785	.4080	1.1283
21 - 30	-.2036	.2167	.8158	.5335	1.2475
31 - 40	.2061	.2158	1.2276	.8042	1.8740
41 - 50	-.2926	.2687	.7463	.4403	1.2637
50 +	-.5052	.8587	.6034	.1659	2.1943

TABLE No.6

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 10 YEARS

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0100	.0417	.9900	.9123	1.0744
SELF RESPONDENTS	.0526	.0510	1.0540	.9537	1.1648
SURROGATE RESPONDENTS	-.1423	.0754	.8674	.7483	1.0054
NEVER SMOKERS	-.0336	.0633	.9670	.8541	1.0948
FORMER SMOKERS	.0082	.0560	1.0082	.9034	1.1252
FEMALES	.0020	.0610	1.0020	.8892	1.1292
MALES	-.0207	.0520	.9798	.8846	1.0847
EPIDERMOID/ SMALL CELL	.04017	.0653	1.0410	.9159	1.1832
ADENOCA. & OTHERS	-.0450	.0545	.9560	.8592	1.0638

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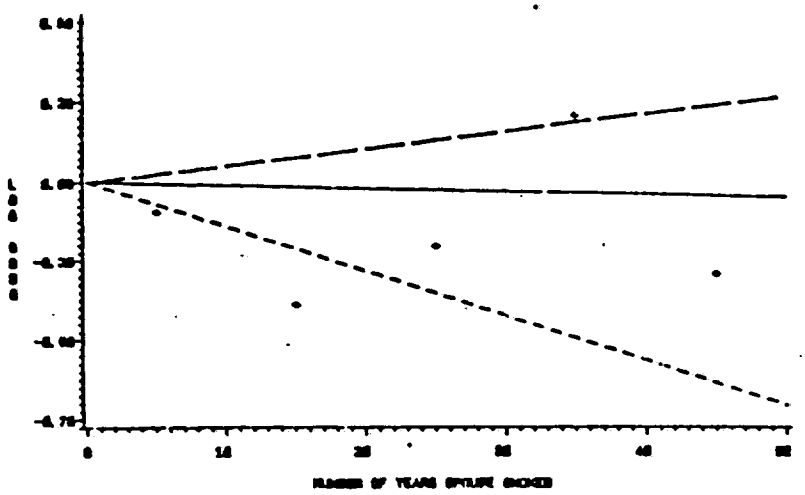
Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No 5

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED, FOR ALL SUBJECTS[a], SELF RESPONDENTS[b], AND SURROGATE RESPONDENTS[b]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]

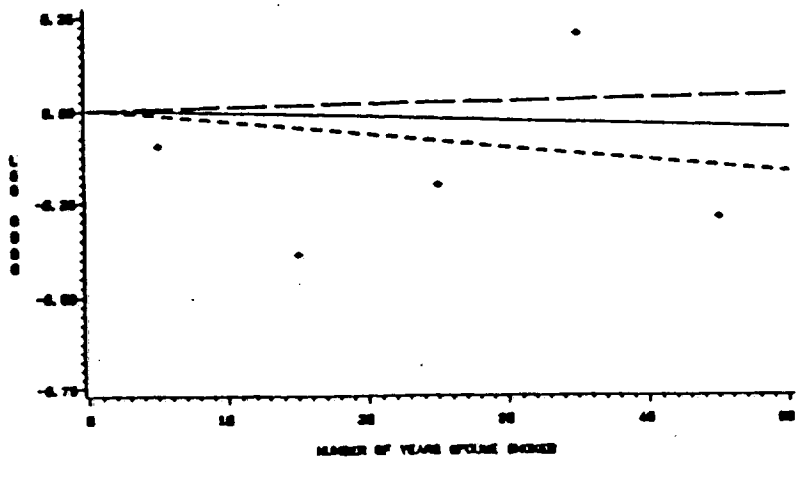


NUMBER OF YEARS SPOUSE SMOKED

[a] CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No 6

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED, FOR ALL SUBJECTS[a], NEVER SMOKERS[b], AND FORMER SMOKERS[b]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]



NUMBER OF YEARS SPOUSE SMOKED

[a] CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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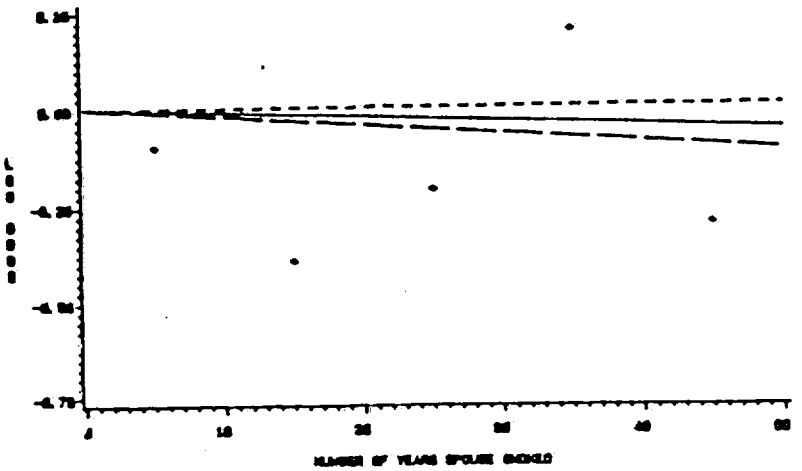
FIGURE No. 7

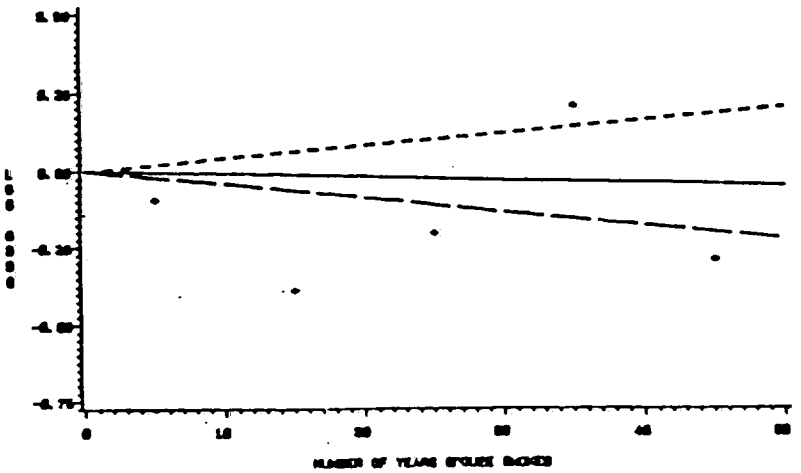
CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 8

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED; FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

TABLE No 7

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO
SPOUSE SMOKING OF 10 YEARS

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0106	.0441	.9894	.9075	1.0788
SELF RESPONDENTS	.0481	.0538	1.0493	.9442	1.1661
SURROGATE RESPONDENTS	-.1325	.0789	.8759	.7504	1.0224
NEVER SMOKERS	-.0330	.0657	.9675	.8507	1.1004
FORMER SMOKERS	.0075	.0590	1.0075	.8976	1.1310
FEMALES	-.0049	.0633	.9951	.8789	1.1266
MALES	-.0158	.0608	.9843	.8736	1.1089
EPIDERMOID/ SMALL CELL	-.1151	.0951	.8913	.7397	1.0739
ADENOCA. & OTHERS	-.0617	.0604	.9402	.8351	1.0584

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the inclusion of confounding variables causes a change in the sign of the estimates for females and for epidermoid tumor type. This change, however, is not accompanied by a change in the test of significance.

3.1.3 TOTAL NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE.

Although already described in the previous chapter, it is important once again to emphasize at this point the manner in which the total number of cigarettes smoked by the subject spouse(s) during married life was calculated: the number of cigarettes smoked per day was multiplied by 365 to obtain the total number of cigarettes smoked in a year. This amount was then multiplied by the number of years of marriage or the number of years of cohabitation. If there was more than one spouse, the figures for each were added up into a single total measurement of exposure. The resulting figures can be numbers on the order of the hundreds of thousands. This may surprise the reader of this report, however, it must be mentioned that these seemingly high numbers do not in fact represent unusual exposures. For instance, a subject married during 35 years to a smoker of 1 pack of cigarettes per day would be exposed to over 250,000 cigarettes over the course of his/her married life (20 cigarettes/day X 365 days X 35 years).

The total number of cigarettes smoked by the spouse was first evaluated as a categorical variable. The categories used were chosen to be identical to those used by Trichopoulos in his study of Greek

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women. The estimates of the effects for the 5 categories assessed are presented in Table No 8. The first four estimates, corresponding to exposures of up to 400,000 cigarettes, show a negative sign, suggesting that the effects may be contrary to the hypothesized. Viewed statistically, however, these values are not significantly different from the null value, as demonstrated by the confidence intervals also presented in Table No 8. The fifth estimate, corresponding to an exposure of more than 400,000 cigarettes (OR = 1.046), suggests a small risk above the risk for the non-exposed. But again, this figure does not reach statistical significance (95% CL: .6532 - 1.6762). The plot that presents the estimates of effect for the five categories in a logarithmic scale (Figure No 9) suggests that a test of linear trend should be performed. The parameter representing this linear trend was found not to be significant. Comparing the logistic model for exposure as categories and the model for categories as a linear variable, with the null model of no parameters (i.e. total symmetry model), provided further evidence of no association between exposure and study disease. Neither one showed itself to fit the data better than the null model (ΔG^2 = 1.95, 5 df, and ΔG^2 = .0061, 1 df, respectively).

Exposure, assesed as a continuous variable through a logistic regression model, yielded an estimate of effect equivalent to an odds ratio of 1.0175 for exposure to 200,000 cigarettes during married life (Table No.9). This estimate was found not to be significant, and, as explained in a previous section, indicates that any estimate for higher or lower exposures based on the same logistic model will be

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TABLE No. 8

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO FIVE CATEGORIES OF TOTAL NUMBER OF CIGARETTES SMOKED BY THE SPOUSE(S) DURING MARRIED LIFE.

NUMBER OF CIGARETTES	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1-100,000	-.2029	.1696	.8163	.5630	1.1838
-200,000	-.1377	.2185	.8714	.5678	1.3372
-300,000	-.2130	.2358	.8082	.5091	1.2830
-400,000	-.0782	.3087	.9247	.5050	1.6935
400,000 +	.04535	.2404	1.046	.6532	1.6762

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TABLE No. 9

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 200,000 CIGARETTES.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.0173	.0757	1.0175	.8772	1.1805
SELF RESPONDENTS	.0964	.0894	1.1012	.9242	1.3121
SURROGATE RESPONDENTS	-.2028	.1509	.8164	.6074	1.0973
NEVER SMOKERS	-.0157	.1189	.9844	.7798	1.2428
FORMER SMOKERS	.0399	.0894	1.0407	.8734	1.2400
FEMALES	.0207	.1000	1.021	.8393	1.2420
MALES	.1274	.1096	1.1359	.9163	1.4081
EPIDERMOID/ SMALL CELL	.0536	.1221	1.0551	.8306	1.3403
ADENOCA. & OTHERS	-.0055	.1096	.9946	.8023	1.2329

FIGURE No. 9

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*, AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

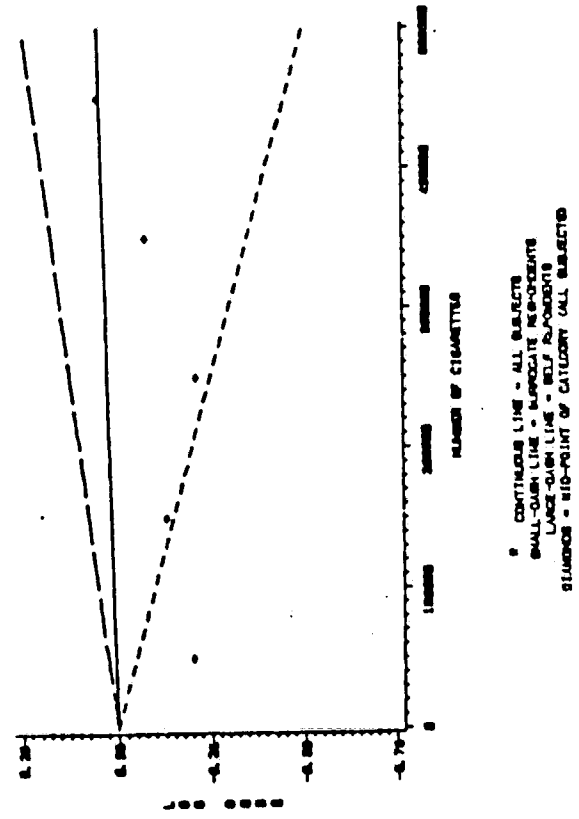
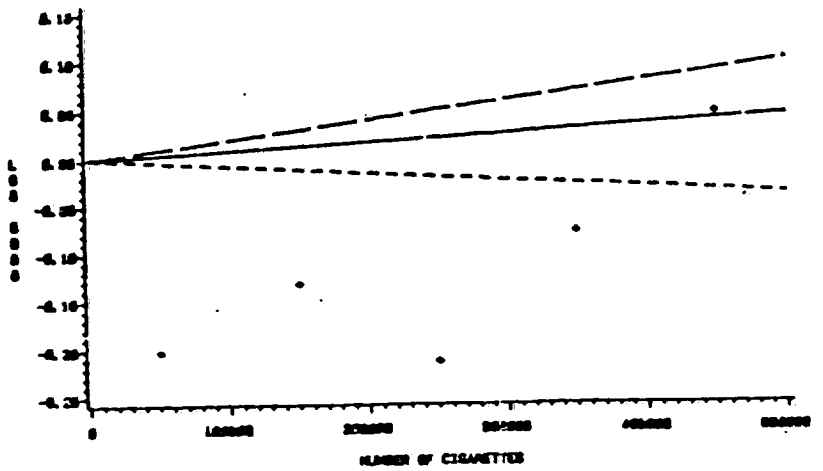


FIGURE No. 10

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

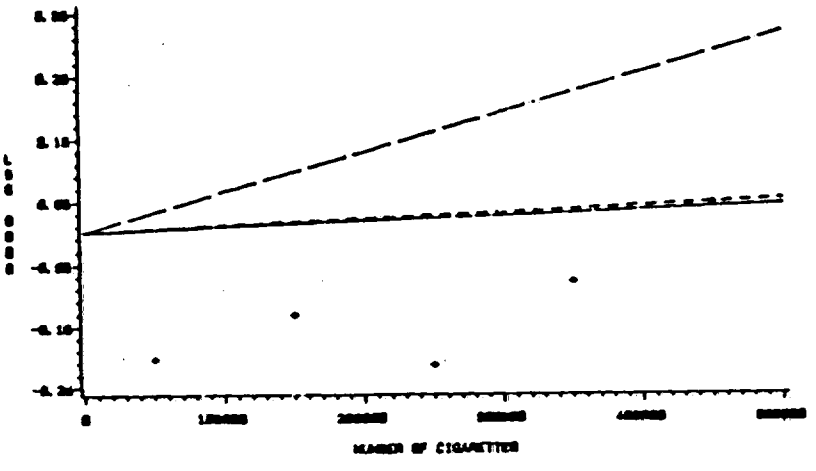


NUMBER OF CIGARETTES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 11

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, FEMALES*, AND MALES*, AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



NUMBER OF CIGARETTES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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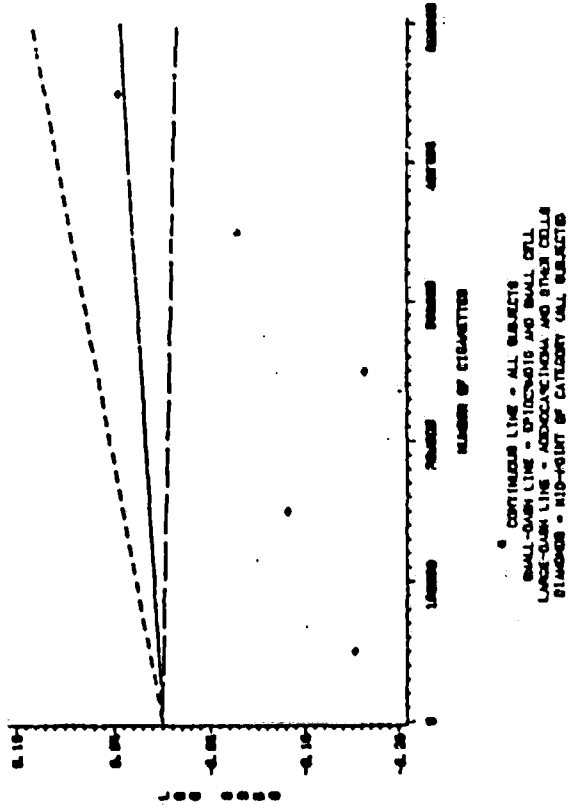
FIGURE No. 12

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES

AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



NUMBER OF CIGARETTES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY ALL SUBJECTS

TABLE No. 10

ADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 200,000 CIGARETTES.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.0128	.0804	1.0129	.8652	1.1858
SELF RESPONDENTS	.0886	.0694	1.0926	.9170	1.3019
SURROGATE RESPONDENTS	-.1897	.1557	.8272	.6097	1.1224
NEVER SMOKERS	-.0212	.1226	.9790	.7699	1.2450
FORMER SMOKERS	.0382	.2460	1.0390	.6428	1.6793
FEMALES	.0067	.1048	1.0067	.8202	1.2357
MALES	.0218	.2190	1.0218	.6652	1.5696
EPIDERMOID/ SMALL CELL	-.1776	.1759	.8372	.5931	1.1818
ADENOCA. & OTHERS	-.0828	.2366	.9205	.5790	1.4636

Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

equally non significant. Also in Table No. 9 estimates for the levels of the stratifyung variables TYPE OF INTERVIEW, SMOKING HISTORY, SEX and HISTOLOGIC DIAGNOSIS do not show significant effects , and in all cases the estimates were not found to be significantly different within levels of the same variable. In-addition to this each of the models that included the interaction between the stratifying variables and the exposure variable did not provide better fit to the data than the models for all subjects, or than the model of total symmetry. An illustration of the lines fitted for all subjects, along with the levels of the stratifying variables, is shown in Figures 9 trough 12.

Finally, the total number of cigarettes smoked during married life was assessed in the presence of confounding variables. Table No 10 shows the estimates obtained and their confidence limits. In no case did the presence of covariates in the model improve the fit to the data or unveil any significant effect of the exposure variable on lung cancer risks.

3.2 PASSIVE SMOKING IN THE HOUSEHOLD.

Cases and controls were questionned about the number of smokers with whom they shared their 12 most recent residences, together with the duration of each cohabitation. The number of smokers in each household, multiplied by the number of years lived in each particular household, and summed over the 12 residences, estimates the number of person/years of exposure to passive smoking.

Inspection of the raw data showed that for some of the 12 residences — particularly those corresponding to early stages in life — the information on the number of smokers in the household was missing. The data was analyzed in two ways, each making a different assumption about these missing values. Under the first assumption we assumed that one smoker had lived in the households for which information was missing if, that is, there was evidence that the study subject had lived in previous or future residences with at least one other smoker. Under assumption number two it was assumed that there was no exposure (i.e., no smokers in the household) for those residences in which information was missing. Results from analyzing the data under the two assumptions are practically identical. However, both sets of results will be presented to allow the reader to make his/her own conclusions regarding the handling of missing values.

3.2.1. RESULTS UNDER ASSUMPTION 1.

The results of analyzing household exposure as a categorical variable are shown in Table No. 11. Except for the estimate corresponding to 26-50 person/years of exposure (OR=.9154, 95% CL: .5510 - 1.5208), all point odds ratios suggest an increased risk of lung cancer associated with household exposure to passive smoking. However, only the highest exposure — which also produces the highest estimate of effect — shows evidence of statistical significance (OR for exposure to +175 person/years= 2.85 (95% CL: 1.09 - 7.42]). Still, the plot of the eight estimates presented in Figure No 13 suggests that a linear model may be adequate to describe the relationship between the categories of

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

exposure and the risk of disease. In the usual manner, a variable reflecting linearity in the levels of the categories (the case-control difference of the midpoints of the categories) was entered in the regression model. The resulting model showed to be significantly different from the model with no parameters (ΔG^2 = 9.01, 1 df). In addition, the estimate representing the slope for the fitted line was found to be significantly different from zero (estimate= .004485, Wald= 2.95). The comparison of the model for the categories with the model for the "linear" categories did not provide evidence of departure from linearity (ΔG^2 = 5.87, 7 df). A higher order model with a quadratic term was fitted to the data but it was found not to be significant.

The model fitted to the data to assess the effect of exposure as a continuous variable yielded estimates that support the existence of an association between exposure and study disease. The odds ratio associated with 150 person/years of exposure was 1.856, with lower (1.218) and upper (2.830) 95% confidence limits well above the null value (See Table No 12).

Using the same model we can estimate the odds ratio associated with a very high exposure of 250 person/years as varying between 1.389 and 5.66, as indicated by the point estimates confidence limits.

The effect of household smoking according to TYPE OF INTERVIEW does not show differences in the effect for self-respondents versus surrogate respondents (Table No 12). However, when SMOKING HISTORY is

considered, the effect for never smokers is not significant, whereas the effect for former smokers is. This finding is all the more puzzling because both estimates are almost identical in value and because the test of interaction suggests that they are not significantly different from each other. The effect for each of the two sexes is also estimated to be very close to one another. In this case, however, both are significant and not different from each other.

A higher effect of household passive smoking was found associated with epidermoid and small cell histologic types (OR=2.83) than for adenocarcinoma and other cell types (OR=1.42). Moreover, the effect for epidermoid type is significant (95% CL: 1.39-5.76), whereas the effect for adenocarcinoma is not (95% CL: .835 - 2.41). Figures No 13 - 16 illustrate the lines for the regression models for each of the subgroups described above.

The model that assesses the effect of household exposure in the presence of confounding variables yields results that are different from the results of the model without such variables (Table No 13). The estimate of effect for the whole group is slightly lower (OR = 1.556), but no change is observed in its statistical significance (95% CL = 1.0006 - 2.42). The estimates for surrogate respondents, self-respondents, former smokers, males, females, and epidermoid histologic type -- formerly significant -- do have confidence intervals (in the presence of covariates) that include the null value, and point estimates which suggest lesser effects than the unadjusted estimates. The point estimate for adenocarcinoma (OR=1.87), although still lower

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TABLE No. 11

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF SMOKING IN THE HOUSEHOLD *

PERSON/YRS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 25	.1269	.2815	1.1353	.6539	1.9712
26 - 50	-.0884	.2590	.9154	.5510	1.5208
51 - 75	.4514	.2661	1.5705	.9322	2.6458
76 - 100	.4437	.2922	1.5585	.8790	2.7633
101 - 125	.2795	.3139	1.3225	.7148	2.4467
126 - 150	.5194	.4595	1.6810	.6830	4.1372
151 - 175	.5368	.4490	1.7105	.7095	4.1241
175 +	1.0460	.4887	2.8462	1.0922	7.4176

*Results under assumption 1. See text for details.

TABLE No. 12

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE HOUSEHOLD *

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	0.6186	0.2151	1.8563	1.2178	2.8298
SELF RESPONDENTS	.5469	.2625	1.7279	1.0329	2.89041
SURROGATE RESPONDENTS	.7632	.3774	2.1451	1.0238	4.4947
NEVER SMOKERS	.61065	.3186	1.8416	.9863	3.4387
FORMER SMOKERS	.6252	.2918	1.8686	1.05482	3.3103
FEMALES	.6258	.3120	1.8697	1.0144	3.4464
MALES	.6120	.2970	1.8441	1.0303	3.3006
EPIDERMOID/ SMALL CELL	1.0395	.3626	2.8278	1.3894	5.7552
ADENOCA. & OTHERS	.34935	.2700	1.4182	.8354	2.4074

*Results under assumption 1. See text for details.

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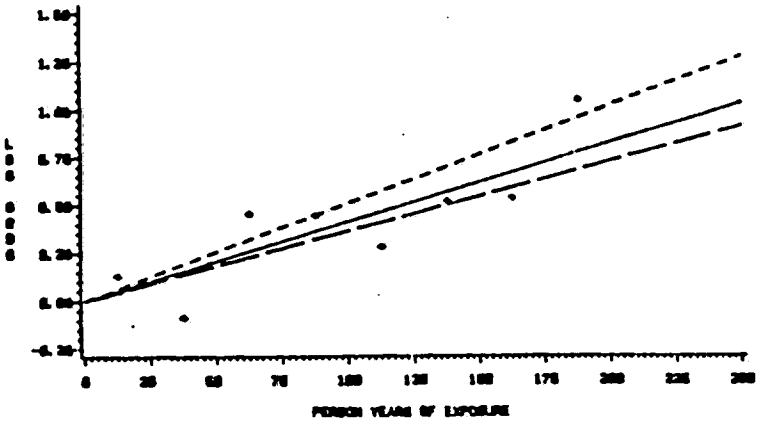
FIGURE No. 13

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD*, FOR ALL SUBJECTS*, SELF RESPONDENTS *, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

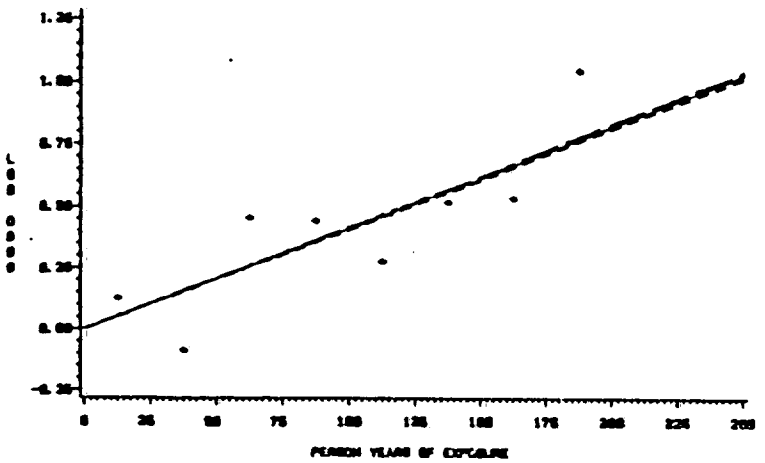


*Results under assumption 1. See text for details.

CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 14

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD*, FOR ALL SUBJECTS*, NEVER SMOKERS *, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



*Results under assumption 1. See text for details.

CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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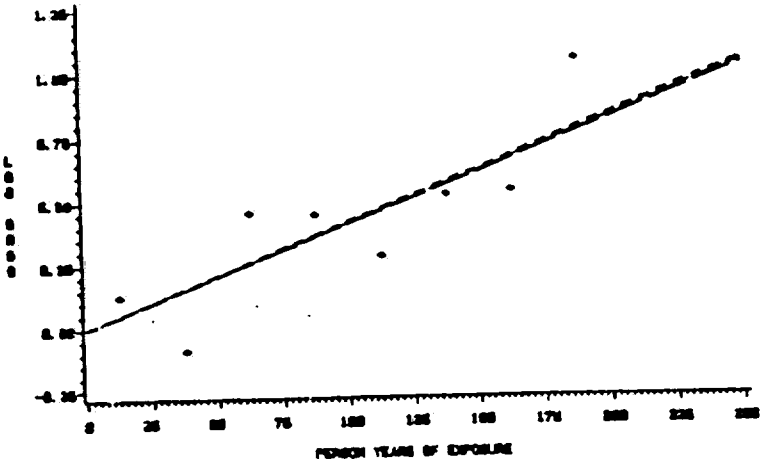
Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No. 15

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE
TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[A],
FEMALES[@], AND MALES[@];
AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[@]

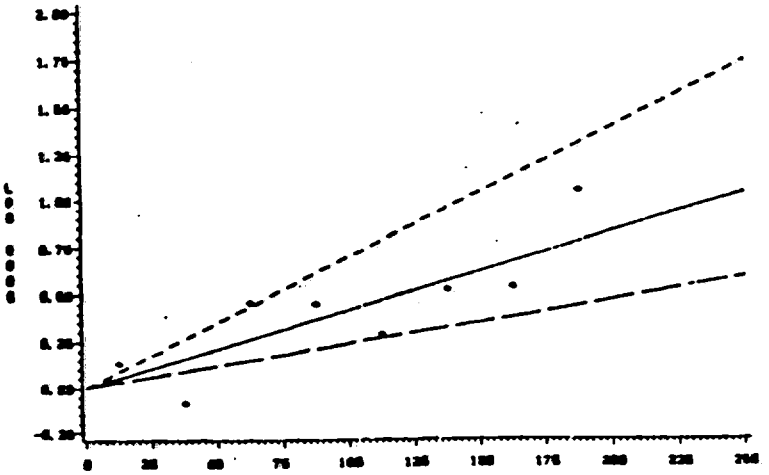


@Results under assumption 1. See text for details.

@ CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTED)

FIGURE No. 16

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE
TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[@],
EPIDERMOID/SMALL CELL[@], AND ADENOCARCINOMA/OTHER[@];
HISTOLOGIC TYPES
AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[@]



@Results under assumption 1. See text for details.

@ CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTED)

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

TABLE No. 13

ADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE HOUSEHOLD ●

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.4422	.2253	1.5561	1.0006	2.4200
SELF RESPONDENTS	.3238	.2764	1.3824	.8041	2.3766
SURROGATE RESPONDENTS	.6726	.3937	1.9593	.9056	4.2391
NEVER SMOKERS	.3753	.3093	1.4554	.7938	2.6685
FORMER SMOKERS	.5157	.3266	1.6748	.8831	3.1764
FEMALES	.4239	.3256	1.5279	.770	2.8926
MALES	.4585	.3090	1.5817	.8631	2.8986
EPIDERMOID/ SMALL CELL	.8428	.5008	2.3230	.8704	6.1998
ADENOCA. & OTHERS	.6248	.3188	1.8678	1.0000	3.4886

●Results under assumption 1. See text for details.

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than the estimate for epidermoid type (OR=2.32), takes on a borderline significant value.

3.2.2 RESULTS UNDER ASSUMPTION 2.

Table No 14 presents the results of analyzing household exposure as a categorical variable when household exposure was calculated under assumption 2. Except for the first two estimates, all suggest an increased risk for lung cancer among the exposed. The plot of the estimates (Fig No 17) also seems to suggest that the risk increases with increasing exposure. While none of the estimates is significant (see confidence limits in the table), the linear trend is (ΔG^2 = 7.014, 1 df, going from the model with no parameters to the model with the regressor representing a linear trend for the categories). Thus, in comparison with the estimates obtained under assumption 1, the present estimates only differ in the non-significance of the estimate for the highest exposure. When analyzed as a continuous variable (Table No 15 the estimate of effect (OR= 1.73 for 150 person/years of exposure) is slightly lower than the effect obtained under assumption 1 (OR = 1.856). However, their confidence intervals overlap to a considerable degree (95% CL: 1.218 - 2.83 and 1.137 - 2.640. respectively). Significant effects were found for only two of the subgroups analyzed, former smokers (OR = 1.770 , 95% CL: 1.0008 - 3.132) and epidermoid histologic type (OR = 2.585, 95% CL: 301 - 5.137). Inclusion of confounding variables in the model (Table No 16) results in non-significant effects for these and the other subgroups, as well as for the group that comprises all subjects

Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

TABLE No. 14

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF SMOKING IN THE HOUSEHOLD*

PERSON/YRS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 25	-.0958	.2669	.9087	.5386	1.5332
26 - 50	-.2604	.2410	.7707	.4806	1.2361
51 - 75	.2884	.2478	1.3343	.8210	2.1686
76 - 100	.2451	.2839	1.2778	.7326	2.2290
101 - 125	.1030	.2972	1.1085	.6191	1.9848
126 - 150	.6191	.4547	1.8573	.7618	4.5291
151 - 175	.2093	.4513	1.2328	.5090	2.9857
175 +	.8521	.4849	2.3446	.9064	6.0648

*Results under assumption 2. See text for details

TABLE No. 15

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE HOUSEHOLD*

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.5492	.2146	1.7318	1.1371	2.6376
SELF RESPONDENTS	.5063	.2622	1.6592	.9924	2.7739
SURROGATE RESPONDENTS	.6356	.3754	1.8881	.9045	3.9410
NEVER SMOKERS	.5226	.3192	1.6864	.9021	3.1526
FORMER SMOKERS	.5712	.2910	1.7704	1.0008	3.1316
FEMALES	.5204	.3102	1.6826	.9181	3.0905
MALES	.5754	.2940	1.7778	.9982	3.1654
EPIDERMOID/ SMALL CELL	.9496	.3504	2.5848	1.3006	5.1368
ADENOCA. & OTHERS	.2802	.2775	1.3234	.7682	2.2798

*Results under assumption 2. See text for details

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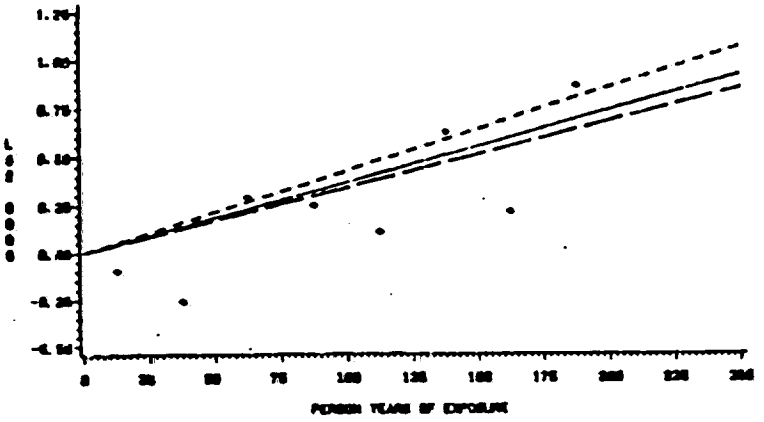
Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No. 17

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD*, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

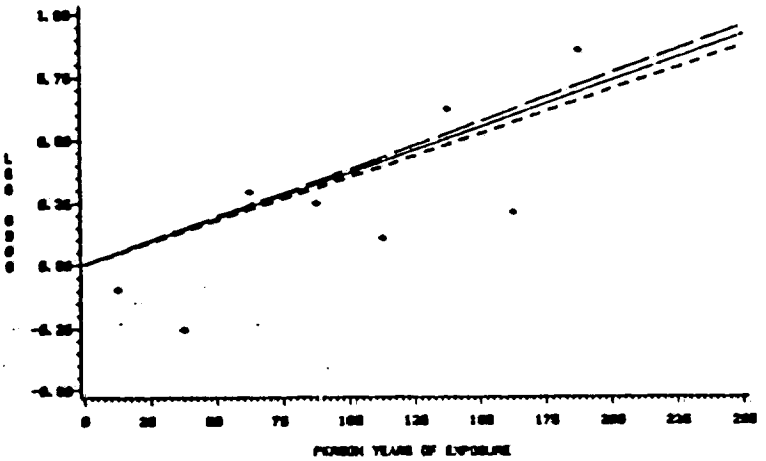


*Results under assumption 2. See text for details.

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 18

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD*, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



*Results under assumption 2. See text for details.

CONTINUOUS LINE = ALL SUBJECTS
* SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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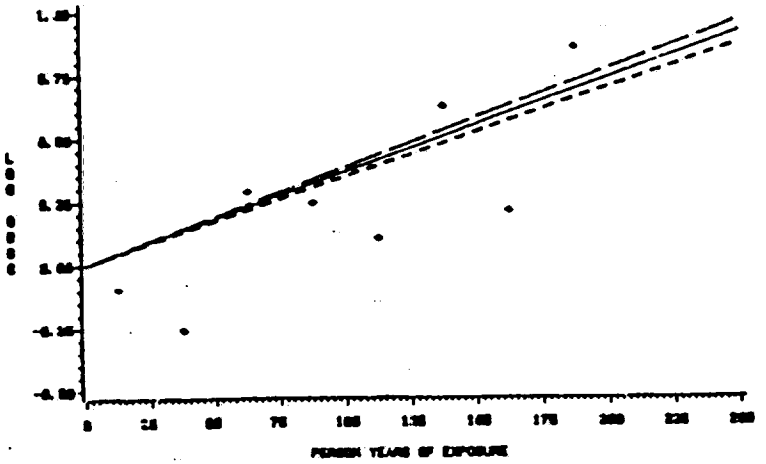
Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No. 19

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[a], FEMALES[a], AND MALES[a]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]

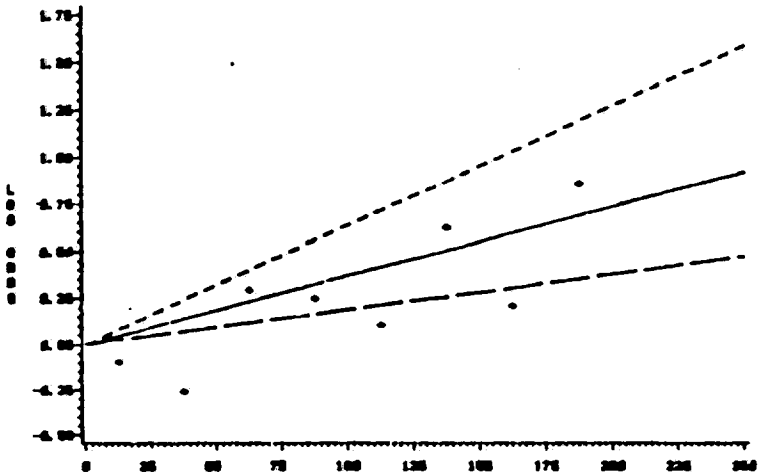


@Results under assumption 2. See text for details.

a CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 20

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[a], EPIDERMOID/SMALL CELL[a], AND ADENOCARCINOMA/OTHER[a]; HISTOLOGIC TYPES AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]



PERSON YEARS OF EXPOSURE

a CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

@Results under assumption 2. See text for details.

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

TABLE NO. 16

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
150 PERSON/YEARS SMOKING IN THE HOUSEHOLD @

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.3732	.2252	1.4624	.9342	2.2580
SELF RESPONDENTS	.2818	.2763	1.3256	.7713	2.2782
SURROGATE RESPONDENTS	.5510	.3906	1.7349	.8068	3.7304
NEVER SMOKERS	.4332	.3256	1.5422	.8146	2.9197
FORMER SMOKERS	.3186	.3091	1.3752	.7503	2.5204
FEMALES	.3112	.3240	1.3651	.7240	2.5739
MALES	.4293	.3101	1.5362	.8365	2.8212
EPIDERMOID/ SMALL CELL	.7696	.4988	2.1590	.8123	5.7385
ADENOCA. & OTHERS	.5691	.3165	1.7667	.9500	3.2855

@Results under assumption 2. See text for details

(OR = 1.45, 95% CL: .934 - 2.258).

3.3 EXPOSURE TO SMOKING IN THE WORKPLACE.

Nine categories of smoking in the workplace were created according to different levels of exposure. The values included within each category (except for the referent zero exposure) are shown in Table No 17 under the heading PERSON/YEARS. The interpretation of such units has been explained in the previous chapter in the section that describes the exposure variables

Inspection of the estimates obtained showed effects ranging from odds ratios as low as 0.4664 to odds ratios above the null value (1.187, 1.186, 1.166). None of these is statistically significant (see columns for confidence limits in the table). When these estimates are plotted (Fig. No 21) their distribution in the figure is scattered, thus suggesting no dose-response relationship, the absence of which was confirmed by the non significance of the effect for the variable representing a linear trend for the categories (estimate= -.000287, Wald test= -.2839). Neither the model that assesses exposure as an ordinal categorical variable, nor the model that assesses the linear trend for the categories, provides a better fit to the data than the null model of no association (ΔG^2 = 7.83, 8 df, and ΔG^2 = .084, 1 df, respectively). This further denies evidence for an association between exposure to smoking in the workplace and lung cancer.

The assessment of exposure in the workplace as a continuous

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

TABLE No. 17

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF SMOKING IN THE WORKPLACE

PERSON/YRS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 25	-.2091	.2006	.8113	.5477	1.2019
26 - 50	.1705	.2513	1.1859	.7247	1.9407
51 - 75	.1536	.3083	1.1660	.6372	2.1337
76 - 100	-.6531	.4402	.5762	.2427	1.3630
101 - 125	.1717	.4548	1.1873	.4869	2.8954
126 - 150	-.3472	.4542	.7067	.2901	1.7212
151 - 175	-.7622	.5176	.4666	.1692	1.2870
175 +	-.0377	.2141	.9630	.6330	1.4652

TABLE No. 18

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE WORKPLACE

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0060	.0104	.9941	.9740	1.0145
SELF RESPONDENTS	.0138	.0170	1.0139	.9806	1.0483
SURROGATE RESPONDENTS	-.1108	.1249	.8951	.7008	1.1433
NEVER SMOKERS	-.05329	.0649	.9481	.8348	1.0767
FORMER SMOKERS	-.0047	.0105	.9953	.9751	1.0160
FEMALES	-.3140	.0817	.8691	.8257	1.1374
MALES	.0055	.0105	1.006	.9851	1.0265
EPIDERMOID SMALL CELL	-.0068	.0124	.9912	.9674	1.0156
ADENOCA. & OTHERS	.0037	.0223	1.0037	.9608	1.0484

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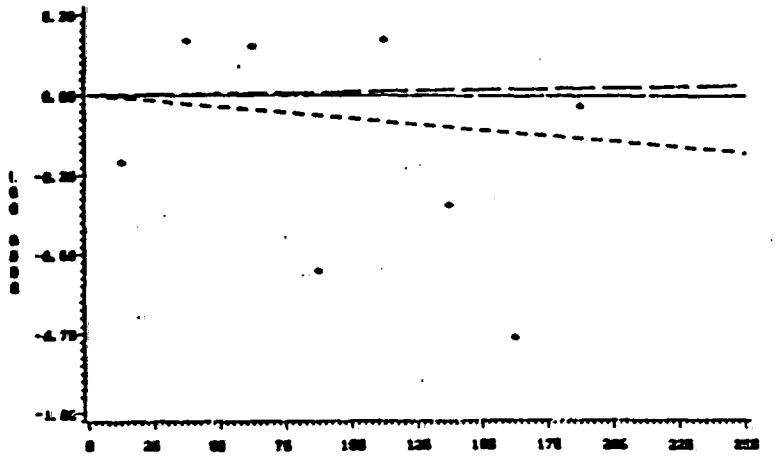
Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No 21

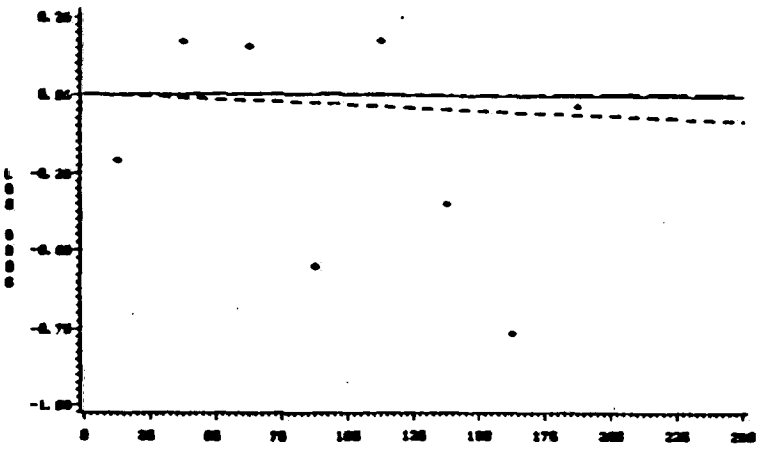
CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*, AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 22

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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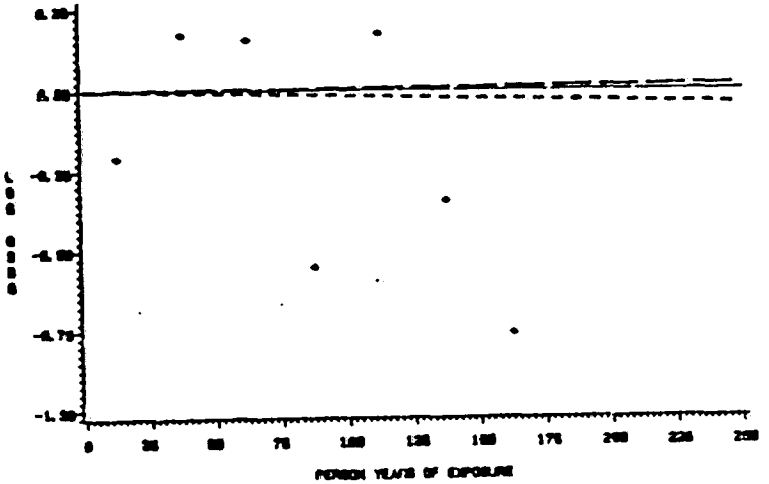
Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No. 23

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

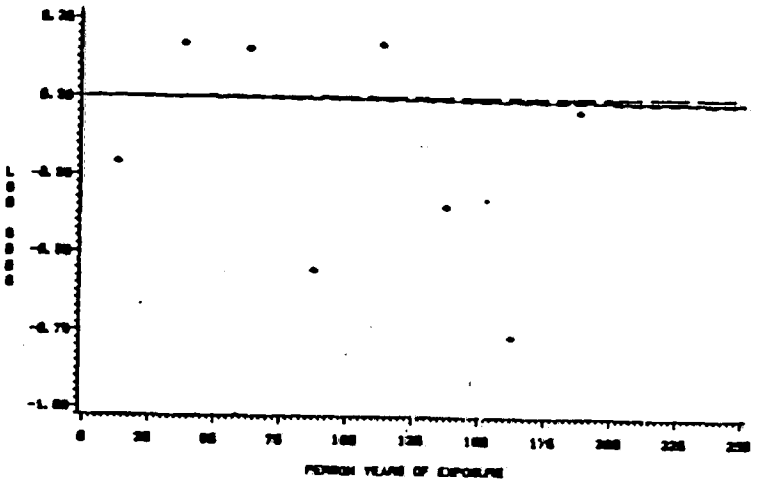


PERSON YEARS OF EXPOSURE

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTED)

FIGURE No 24

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



PERSON YEARS OF EXPOSURE

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTED)

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

TABLE No 19

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
150 PERSON/YEARS SMOKING IN THE WORKPLACE

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0101	.0106	.9900	.9797	1.0107
SELF RESPONDENTS	.0105	.0170	1.0106	.9775	1.0446
SURROGATE RESPONDENTS	-.1447	.1345	.8653	.6648	1.1263
NEVER SMOKERS	-.0900	.06716	.9139	.8012	1.0425
FORMER SMOKERS	-.0081	.0104	.9919	.9719	1.0124
FEMALES	-.0541	.0657	.9473	.8009	1.1205
MALES	-.0094	.0105	.9906	.9704	1.0113
EPIDERMOID SMALL CELL	-.0154	.0222	.9847	.9430	1.0285
ADENOCA. & OTHERS	-.0115	0120	.9886	.9656	1.0121

variable supports the findings described for the categorical exposure variable. The odds ratio associated with an exposure of 150 person/years was 0.994, with lower (0.974) and upper (1.014) 95% confidence limits that include the null value (Table No. 18). Moreover, examination of the estimates for the different subgroups defined by the levels of the stratifying variables further support the lack of evidence for an association (lower part of Table No 18 and Figures No 21-24). Likewise, assessment of the effect of exposure obtained from models that include the confounding variables do not provide statistically significant estimates (Table No 19).

3.4 EXPOSURE TO PASSIVE SMOKING IN SOCIAL CIRCUMSTANCES.

Eight categories corresponding to different levels of exposure to passive smoking in social settings were compared to zero exposure through the fitting of a logistic model. Such a model provided a better fit to the data than the model with no parameters (ΔG^2 = 26.41, 8 df). The estimates for the two lowest exposures correspond to odds ratios of 1.838 and 1.064 (Table No. 20). The suggestion of increased risk for lung cancer for these categories of exposure, however, is not supported by the wide confidence limits that include the null value. The six remaining estimates of effect — all non significant — do take negative values; they also seem to indicate a strong linear trend in that direction. Figure No. 25 shows the points suggestive of such linear trend. A test provided the necessary statistical evidence (estimate = -.02263, Wald= - 4.380). In

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summary, by fitting a logistic model to the data that includes exposure as a categorical variable, we found two things: first, that the resulting model fits the data better than a model with no parameters (even though each parameter in the first model is not significantly different from zero), and second, that when categories are made to represent increasing doses of exposure, they show a linear trend opposite to that hypothesized, that is, a decrease in risk with increasing exposure.

The analysis of the index of social exposure to passive smoking as a continuous variable does not change the picture (Table No. 21). Exposure to 20 units of the index of social exposure is accompanied by an odds ratio of 0.699 (95% Confidence limits: 0.5202 - .7850). The estimates for the different levels of the stratifying variables are all close to the value cited above, with confidence limits equally exclusive of the null value. Each of these are shown in the lower part of Table No 21, and the lines representing the linear trends appear in Figures 25 through 28.

Furthermore, the inclusion of confounding variables in the models fitted have very little impact on the values of the point estimates (Table No. 22). The similarity of adjusted and unadjusted estimates is also reflected in overlapping confidence intervals. In two instances, however, the introduction of confounding variables had the effect of yielding non-significant estimates. For surrogate respondents the confidence limits around the odds ratio (0.957) include the null value (0.6424 - 1.426), in the same way as do the confidence limits for the

TABLE No. 20

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF PASSIVE SMOKING IN SOCIAL SITUATIONS

EXPOSURE INDEX	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 10	.6087	.8638	1.8380	.3381	9.9916
11 - 20	.0617	.8644	1.0637	.1954	5.7889
21 - 30	-.1034	.8497	.9018	.1705	4.7684
31 - 40	-.4946	.8538	.6098	.1144	3.2606
41 - 50	-.5363	.8635	.5849	.1077	3.1777
51 - 60	-.5000	.8657	.6065	.1112	3.3094
61 - 70	-1.4440	.9571	.2360	.0362	1.5402
70 +	-1.8700	1.4550	.1541	.0089	2.6693

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TABLE No. 21

UNADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
20 UNITS IN THE INDEX OF EXPOSURE TO SOCIAL PASSIVE SMOKING

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.4478	.1060	.5390	.5202	.7850
SELF RESPONDENTS	-.4614	.1240	.6367	.4993	.8119
SURROGATE RESPONDENTS	-.4386	.1945	.6449	.4405	.9442
NEVER SMOKERS	-.5628	.1591	.5696	.4170	.7781
FORMER SMOKERS	-.3510	.1420	.7040	.5329	.9300
FEMALES	-.8692	.1674	.5121	.3689	.7110
MALES	-.2798	.1380	.7559	.5768	.9907
EPIDERMOID/ SMALL CELL	-.3604	.1786	.6974	.4914	.9898
ADENOCA. & OTHERS	-.4926	.1300	.6110	.4736	.7884

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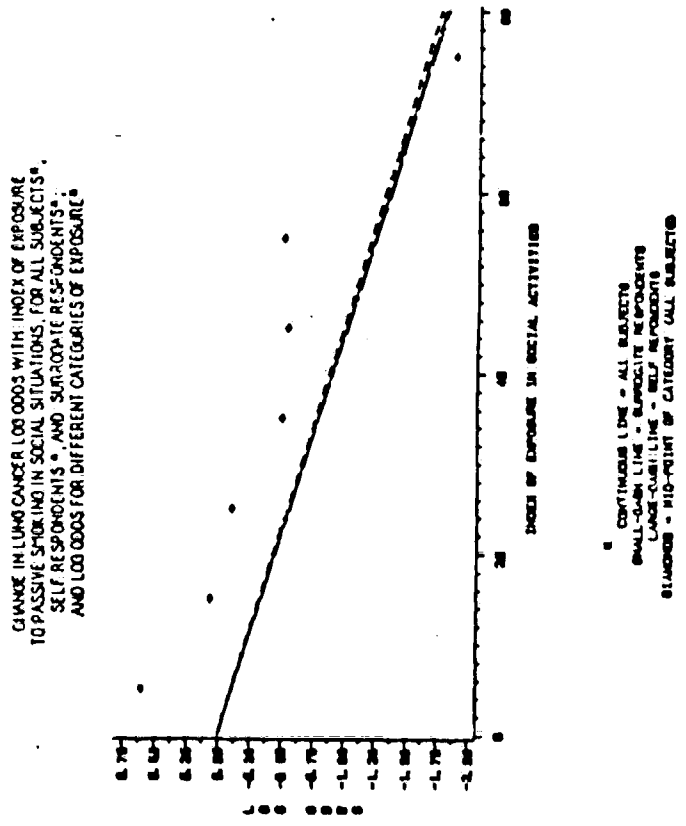


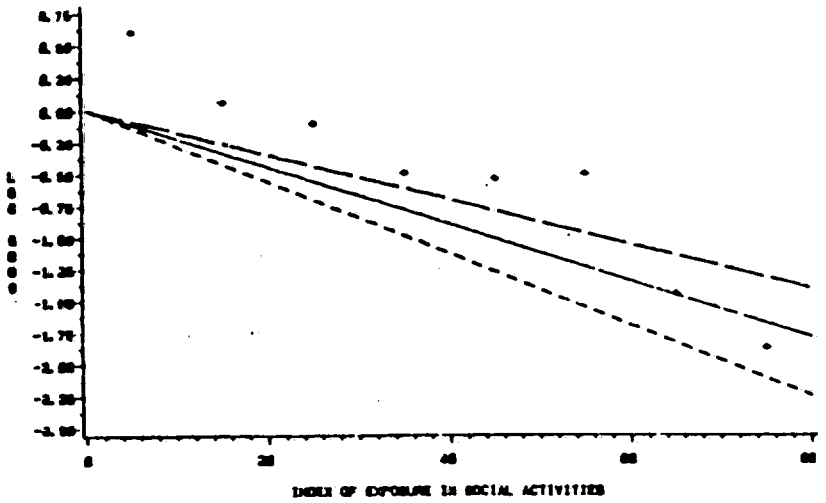
FIGURE No. 25

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

FIGURE No. 26

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

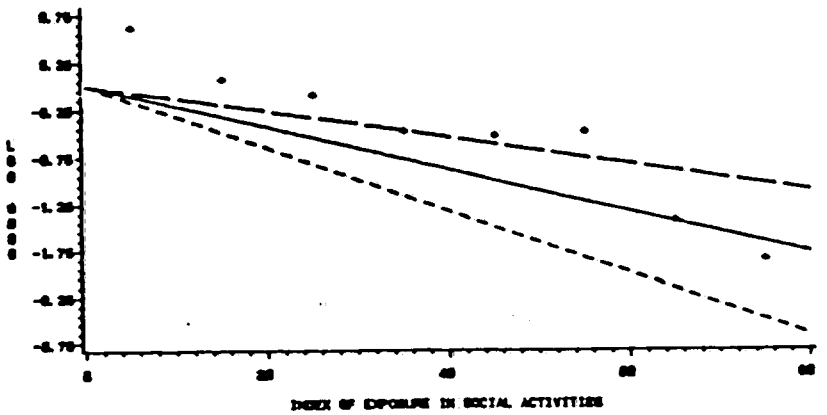


INDEX OF EXPOSURE IN SOCIAL ACTIVITIES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 27

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



INDEX OF EXPOSURE IN SOCIAL ACTIVITIES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/hjyx0000

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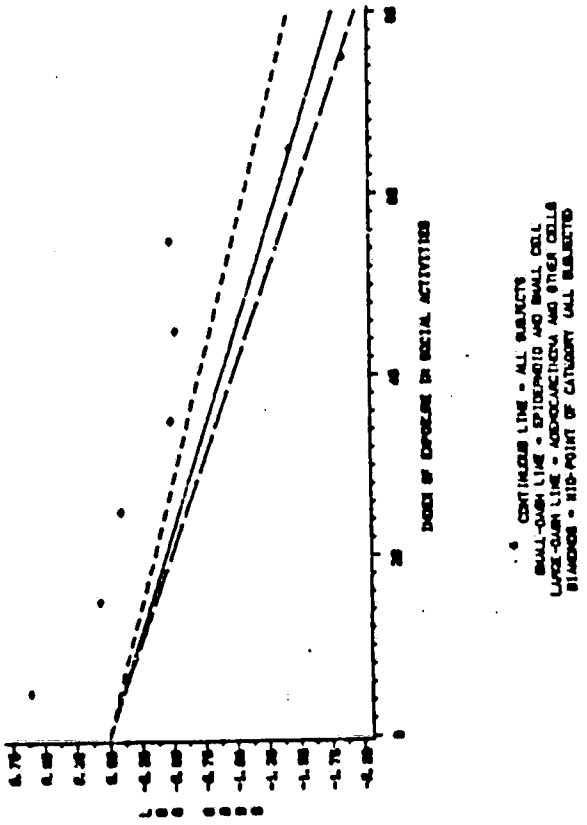
FIGURE No. 26

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*, HISTOLOGIC TYPES

AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



INDEX OF EXPOSURE TO SOCIAL ACTIVITIES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

TABLE No. 22

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
20 UNITS IN THE INDEX OF EXPOSURE TO SOCIAL PASSIVE SMOKING

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.4694	.1107	.6254	.5034	.7769
SELF RESPONDENTS	-.4816	.1305	.6178	.4783	.7979
SURROGATE RESPONDENTS	-.0439	.2034	.9571	.6424	1.4259
NEVER SMOKERS	-.5310	.1626	.5880	.4275	.8086
FORMER SMOKERS	-.4141	.1512	.6609	.4914	.8890
FEMALES	-.6806	.1714	.5063	.3619	.7084
MALES	-.2990	.1485	.7416	.5544	.9923
EPIDERMOID/ SMALL CELL	-.3020	.2418	.7393	.4603	1.1876
ADENOCA. & OTHERS	-.3963	.1443	.6728	.5070	.8928

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estimate for epidermoid histologic type does (OR = .7393, 95% Confidence limits: 0.4603 - 1.188).

CHAPTER FOUR

DISCUSSION

The hypothesis that lung cancer may be etiologically associated with exposure to environmental tobacco smoke has only recently received attention from epidemiologists and other scientists. The possibility of such an association had been raised in the early 1970's, but it was not until this decade that the first population studies addressing this issue were published. The scientific and, above all, the political ramifications of the subject seemed to demand quick answers. It is not surprising, then, that some of the first reports did not come from studies specifically designed to evaluate the purported association. They were the result of cleverly analyzed information that had been collected for other purposes. These studies were very valuable in throwing some light on the degree of the suspected association, but also they suffered from methodologic drawbacks that cast some doubt on the reliability of their results. Later studies have provided further and more specific information.

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However, the complex nature of the problem, along with the imperfection of present research tools, have precluded the establishment of definite conclusions. As it is almost always the case in epidemiologic research, it is the information from many different studies that will provide the evidence necessary either to reject or to accept the existence of the association. The present study was carried out to further assess the relationship between passive smoking and lung cancer, as well as to provide answers to some of the methodological problems encountered by other authors. In this chapter I will present a discussion of the general aspects of the study that may have had an effect on our results, such as sample size, composition of our study population (i.e. inclusion of both sexes, inclusion of former smokers, etc.), approach to data collection, choice of statistical techniques, and so on. This will be followed by a more specific discussion of the results of each of our exposure variables, focusing on the way in which these results compare with others previously reported.

The present study is to date the largest ever conducted on this subject. The implication of this fact reflects on the improved statistical power of our study over other studies with regard to their ability to detect differences in risk between the exposed and the unexposed. When the estimate of effect is expected to be moderate or small, as has been the case as suggested by previous epidemiologic and laboratory studies, consideration of sample size takes on special importance. Our estimation of sample size required to detect an effect of the order reported independently by Hirayama and Trichopoulous

resulted in a figure of 450 case-control pairs, given that a matched design would be used. We were able to assemble 439 pairs that met the eligibility criteria fully. A sample of this size provides a a close to 95% probability of correctly rejecting the null hypothesis (power calculation based on an odds ratio of 2.0; proportion of exposed controls to spouse smoking, p, of 0.25; and significance level, α, of

It has been suggested that the estimates found by Hirayama and Trichopoulous are too high, in light of what is known about smoke uptake by non-smokers (the uptake has been estimated to be equivalent to the smoking of 0.1 to 1.0 cigarette per day [65]). It follows that the use of such estimates would overestimate the power of any given sample size. An odds ratio of 1.3 is believed to reflect more accurately the risk associated with the level of exposure attained by passive smoking (65). When we use the latter estimate to calculate the statistical power of our sample size, the resulting figure is still higher than the conventionally accepted 80%. Furthermore, when in these calculations we change the value of the proportion of the exposed controls from 0.25 to 0.50 (the proportion of exposed controls actually observed in our study), our statistical power increases above 90%.

The difficulty in gathering a large enough number of cases for study derives from the fact that most lung cancer cases occur among smokers. Even though the latter are probably exposed to large amounts of environmental tobacco smoke as a consequence of both their own smoking and their association with other smokers, they are unsuited

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for a study of the effects of passive smoking, since their own habits would tend to mask any effect due to environmental smoke. We recognized that the ideal group to be studied was a group of never smokers. It became evident, however, that the population we were working with would not yield enough never smoking cases in any practical period of time. Instead of reducing our sample size at the expense of statistical power, it was decided to include ex-smokers in the study. The major prospective studies (90-91) have shown that the risk of lung cancer among former smokers can decrease, after 15 to 20 years, to a point where it resembles the risk of the never smokers. On the average the ex-smokers included in our sample had quit 18 years prior to their participation in the study. We were aware, nonetheless, that some residual effect of past smoking habits might still show in our data and thus confound the effect due to passive smoking.

We took three steps to ensure that our conclusions would not be affected by the inclusion of former smokers. These are: 1) the design of the study established that cases and controls should be matched on the basis of smoking history, 2) separate estimates of effect were obtained for smokers and former smokers, and 3) we controlled in the analysis for a variable that represented the number of cigarettes the ex-smokers used to smoke per day. Our results provided evidence that the inclusion of former smokers was not inappropiate. In no case did we find differences in the estimates of effect between never and former smokers which were statistically significant. Nevertheless, a residual effect due to past smoking habits was found. Former smokers

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of 1 pack of cigarrettes/day showed a statistically significant odds ratio of 1.38. It should be emphesized that this effect was controlled for in the analysis (as explained in number 3, above) and therefore is not to be viewed as responsible for any effect found for passive smoking.

Most researchers have restricted their studies on passive smoking exclusively to women. This is again related to the fact that it is easier to find non-smoking lung cancer cases among women than among men. In this choice it is implied to a certain extent that results can then be extrapolated to men. That is, it is assumed that men are as susceptible to environmental smoke as women, although this is not as easily observed in a male population because men acquire lung cancer as a consequence of their own smoking. While this proposition makes sense, we felt that it deserved to be evaluated. The finding of an association in males would strengthen the evidence of the carcinogenic effect of environmental smoke. Our study includes also the largest series of male non-smoking lung cancer cases (28.5% of these are never smokers and 71.5% are former smokers).

Our cases were drawn from all diagnostic and treatment facilities operating in the study area. Further checks for cases were performed at the New York State Tumor Registry. Except for a few cases who may have left the area in order to get medical care in other regions, we are confident of having detected all incident cases occurring during the study period. Our response rate of 76% can be considered good for most conventional standards. We do not have detailed information on

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the characteristics of the individuals who refused to participate, but it is the impression of the field research assistants that the reasons for refusal were more of a medical nature — i.e. the case was too ill to participate — rather than associated with any particular sociodemographic characteristics.

Correct classification of the study subjects according to their smoking history is crucial in studies on passive smoking. Inclusion of current smokers would spuriously increase the risk for the study disease. When smoking status of the reported cases was ascertained as part of determining elegibility for participation in our study, only those reported in the medical records as former smokers, never smokers or of unknown smoking status were contacted by telephone to further confirm their smoking histories . In addition to this, the research assistant would at the time of the interview further question these subjects in this regard . The need to confirm the smoking history stated in medical records is best illustrated by Garfinkel's findings (30). In that study close to 40% of the women with lung cancer classified as non-smokers (or smoking status not stated) on the hospital records, had been smokers at some time. In our study no attempt was made to confirm the smoking history of those reported as smokers, or even to establish contact with them. It seems less likely, however, that a former or a never smoker would report him/herself as a current smoker, thus escaping inclusion into the study.

The close scrutiny of our cases and controls regarding their

smoking histories strongly indicates that misclassification was not a likely event. Previous studies have been questioned in this regard. The relatively high lung cancer mortality among non-smoking women as compared to smoking women in Hirayama's study (25), as well as the high mortality for other tobacco-related diseases, have suggested that some smoking women may have reported themselves to belong to the non-smoking group. This would not be surprising in a traditional society such as Japan. The consequences of such misclassification would be to overestimate the effect due to passive smoking.

The Greek study (27) can also be criticized on the same grounds. The claim that more than 75% (40 out of 51) of lung cancer cases were diagnosed among non-smoking women is inconsistent with the proportion reported in the literature. It is considered that only about 10% of all lung cancer in women ocurrs in non-smokers (the corresponding figure for men is 2.0%). It is therefore likely that this study confounded the effect of passive smoking with the effect due to direct cigarette smoking, at least to a certain degree.

Before our study, only Garfinkel and coworkers (30) had carried out an independent review of the histologic diagnoses of cases. In most other reports the authors had relied on the discharge diagnoses recorded in the patient's medical records. The degree to which those diagnoses were based on examination of pathology specimens is varied. In Trichopoulous' study only 35% had an histologic diagnosis (27). The corresponding figure for Akiba's study is 57% (32). Pelayo Correa reports 97% (29). Both Hirayama's work and Garfinkel's first study

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using the American Cancer Society data relied exclusively on death certificates (24-25). The importance of histologic diagnoses is that it provides the most accurate measurement of disease status. Inclusion of other cancers can bias the results either away from or towards the null value, depending on whether or not they are related to smoking. The latter is the most likely situation since inclusion of other cancers would tend to be random. An additional advantage of obtaining the histologic diagnosis is that it allows us to estimate the effect for specific histologic types. This is of particular importance to uncover any specificity that would strenghten the evidence of a causal relationship. We were able to obtain almost a 100% of histologic confirmation, and given the excellent agreement between our reviewer and the initial hospital diagnoses we are certain that misclassification of disease status did not play a role in our findings.

Another area of concern in studies of passive smoking refers to the correct classification of study subjects with regard to exposure. In the present study, as in all others that have been published, the study subjects were classified based on the information on exposure obtained through interview. It is acknowledged that this approach is less than ideal. At the moment, however, it is the only feasible option. It has been suggested (as an alternative to interview) that laboratory measurements of cotinine in saliva or blood could be used to determine exposure. These would solve the problem only partially, because such techniques are unfit to measure exposure that has occured troughout a lifetime — a measurement that is necesary when studying

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a disease that probably occurs as a result of a prolonged exposure. Nevertheless, laboratory techniques can be used to validate and refine questionnaires that inquire about exposure.

The problem of recall posed by the use of questionnaires is magnified when the study subjects themselves are not available to provide the necesary information. In our study we had to resort to the use of surrogate respondents in 33.0 % of our interviews. In order to minimize problems arising from this approach we matched cases and controls on type of interview conducted, and obtained separate estimates of effect for self-respondents and surrogate respondents. The results, with only one exception (estimates of effect for number of years smoked by the spouse), did not differ on account of the individual who had provided the information. Similarly, Garfinkel (30) — who only used 12% of direct interviews — did not find significant differences among the different types of informers.

Environmental tobacco smoke has been for the past decades an ubiquituous pollutant to which everybody is believed to have been exposed in different degrees, whether knowingly or unknowingly. It has been suggested, therefore, that all studies on passive smoking suffer from misclassification of exposure since all claim to have identified individuals with zero exposure (that is, the individuals used as the non-exposed referent group). It is impossible to ascertain the degree to which such a problem may be present in our data, as it would be impossible to determine whether or not such a problem — if present — affected cases and controls equally. In the event of

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differential misclassification in our study, we would expect to find bias either away from or towards the null value. If, on the other hand, nondifferential misclassification affected our results, the bias could only be an attenuation of the estimates of effect. For such continuously measured variables as the ones assessed in this study, the magnitude of this bias would depend on the magnitude of the correlation between the true values for exposure and the values of exposure as measured.

We did not obtain information on certain variables known to affect exposure. Ventilation, size of room, proximity to the smoker and other conditions under which smoking takes place influence the actual dose received by the passive smoker. We acknowledge the difficulty in obtaining data in this regard, especially if information about a lifetime is been sought. We also beleived that asking for such extensive detail in a questionnaire might prevent our acquisition of more basic information, by distracting the interviewee from essentials. How these factors may have influenced our results can not finally be determined.

All our controls came from the files of the New York State Department of Motor Vehicles. We have data to support that they are comparable to the cases in the most relevent characteristics. There is, however, one potential source of problems. Whereas we are certain, by definition, that all controls were licensed drivers, we do not know the cases' status with regard to driving. If driving status is somehow related to the risk of lung cancer either directly or, much more likely, indirectly, our results might have been subject to bias.

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However, if any possible differences in driving status reflect only differences in socioeconomic status, our controlling in the analysis by INCOME should have taken care of the problem.

Of all the measures aimed to assess exposure to passive smoking, some measurement of the spouse smoking habits has been the most frequently used. This may account, at least partially, for the fact that this is also the measure most often reported to show a positive association with lung cancer risk. Among the different ways in which spouse smoking has been quantified, the number of cigarettes smoked per day appears most often in the literature. Number of packs a year smoked, total number of cigarettes smoked in a lifetime, number of years smoking, and number of cigarettes smoked at home have also been used as a proxy for exposure to passive smoking. In the present study we have chosen three different measurements of exposure: 1) number of cigarettes smoked a day by the spouse, 2) number of years the spouse smoked, and 3) total number of cigarettes smoked while married and living together. We beleive these three measurements comprise information on the two most important dimensions of exposure, intensity and duration. Additionaly they also provide results easily comparable to those in other studies.

Previous studies have shown that non-smoking women married to smokers of 20 or more cigarettes a day exhibit a risk of developing lung cancer that is approximately double the risk of those married to non-smokers (25,27,30). The estimates obtained in those studies have been reported to be significant, and when considered along with the

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estimates for other levels of exposure, have also been found to show a dose-response relationship, which further supports the case for a causal relationship. For a somewhat comparable level of exposure we were unable to detect any significant increase in lung cancer risk. Our point estimate of effect for those individuals married to smokers of 21-40 cigarettes/day was an odds ratio of 0.906 (95% CL: .609-1.35), when exposure was analyzed as a categorical variable. For higher levels of exposure we found risks above the null value, but again these findings were not statistically significant. The analysis of exposure data as a continuous variable was consistant with the above results; indeed the effect found for a differential of exposure of 20 cigarettes per day was barely above the null value (OR = 1.011), with confidence limits that include such a figure. Nor there was any evidence of a linear trend.

This report is not the only one that has been unable to confirm a statistically significant association between number of cigarettes smoked by the spouse and lung cancer risks. Akiba, et. al.(32) reported an odds ratio of 1.31 (90% CL: 0.48-3.47) for those exposed to spouse smoking of 20-40 cigarettes/day (reported as 140-279 cigarettes/week). For a similar level of exposure, Dalager et. al. (33) found an odds ratio of 1.5 (95% CL: 0.8-2.7). These latter estimates, although not significant, are within the range of the suspected magnitude of effect. A closer figure to our results, however, was reported by Garfinkel in his analysis of the American Cancer Society Study data (24). For exposure to spouse smoking of 20 or more cigarettes/day he found an odds ratio of 1.10. Similarly his results were not significant.

Our results regarding this variable cannot be accounted for by the inclusion of former smokers since any effect due to this circumstance would act in the opposite direction, that is, would inflate the risk attributable to exposure. Nor can it be explained by the use of surrogate interviews either, since no significant differences were found between the estimates for the latter and the estimates for self-respondents. The effect could not have been diluted by the inclusion of males, since they seem to show a similar response to that of women. Finally, unequal distribution in cases and controls regarding confounding variables cannot be responsible for the findings, as suggested by the minor change the estimates undergo when those variables are included in the analysis.

We did not find an effect dependant on the duration of exposure to passive smoking as measured by the number of years the spouse smoked while married and living together. Two other studies had evaluated the effect attributable to this measure of exposure. Dalager et. al. (33) reported non significant increases in risk due to spouse smoking of 1-20 years (OR = 1.73, 95% CL: .52-5.42), 21-30 years (OR = 1.78, 95% CL: .60-5.10), and >30 years (OR = 1.24, 95% CL: .42-3.53). These figures did not show evidence of a linear trend. Akiba, et. al. (32) reported odds ratios of 2.1 (90% CL: 1.0 - 4.3) for those married to smokers of 1-19 years, of 1.5 (90% CL: 0.8 - 2.7) for those exposed during 20-39 years, and an odds ratio of 1.3 (90% CL: 0.7 - 2.5) for those exposed to 40 or more years. These non significant effects did not show evidence of a linear trend. Garfinkel, et. al incorporated a different measure of duration of

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exposure. They estimated the effect associated with exposure due to husband's smoking in the last 5 and the last 25 years. These measures of exposure were analyzed for different age groups, histologic types, type of respondent, and socioeconomic status. Only one of 30 estimates obtained showed statistical significance (OR = 2.58 for members of the lower middle class exposed to spouse smoking in the last 5 years).

The evaluation of our third measurement of spouse smoking — total number of cigarettes smoked during married life — does not support an association with lung cancer risk. The estimate associated with a differential of exposure of 200,000 cigarettes was found to be 1.018 (95% CL: 0.877 - 1.18). Trichopoulous et. al. (27) used the same measurement to assess passive smoking. Their analysis, however, resulted in estimates that are relatively high (a three-fold increase in risk for exposure to 300,000 - 400,000 cigarettes), and which also show evidence of a linear trend. Their findings persisted after controlling for some important variables. In our study the inclusion of confounding variables did not produce any changes that would reverse our conclusion of a non significant association.

In the paragraphs above we have called attention to the fact that factors related to the design of the study, or to the presence of confounding variables, could not explain the differences between our results and those showing a positive association with spouse smoking. Other circumstances, however, may have affected our results. Some of these are presented as follows.

Critics of the first two epidemiologic studies on passive smoking raised the concern that the results carried out in two foreign countries (i.e. Japan and Greece) might not apply to the U.S. population. Exposure to spouse smoking, it was suggested, would not be as good a proxy measure for overall exposure to smoke in this country as it would be in those more traditional societies. In those societies spouse smoking — it is beleived — not only correlates well with overall exposure, but actually comprises a large proportion of it. A recent study in the U.S. suggests a different picture for this country. Friedman et. al. (92) have found that determining an individuals exposure on the basis of the spouse smoking habits may lead to gross errors. For instance, they reported that 47% of women and 39% of men married to smokers reported zero hours of exposure at home. Conversely, 40.5% of women and 49.2% of men married to non-smokers reported some exposure to the smoke of other persons. The degree in which a similar problem may apply to our data, or the way in which (if present) it may have affected our cases and controls differently, cannot be ascertained through the available information. Thus, such a possibility remains a potential source of error.

Different life conditions in the U.S. may also make the use of spouse smoking a bad proxy for exposure to passive smoking. For instance, the average Japanese home is much smaller than the American home. Two indicators of house size used by the United Nations illustrates this (93) : 1) The average size, represented by the mean number of persons per household, is 3.2 in Japan, whereas in the U.S. is 2.7, and 2) the percentage of housing units with one room only is

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5% in Japan and 1.6% in this country. As mentioned in another section of this report, room size, together with a closely related variable — i.e. proximity to the smoker — greatly influence the exposure dose actually received by the passive smoker.

It might well be argued that, since some recent American studies have supported the findings of Hirayama and Thrichopoulous, objections such as those raised above have already been discounted. It should be emphasized, however, that only the study by Garfinkel et. al. has shown significant findings in the context of research without major methodological problems. An additional study (Pelayo Correa, et. al) presented questionable results, particularly due to the small number of subjects studied. Furthermore the most recent paper published in this country was unable to uncover any statistically significant association (Dalager, et. al.).

The effect due to spouse smoking in our study subjects may be so small as to be undetectable under the present conditions of study. Such effect, however, might well become detectable if exposure from different sources were to accumulate. The fact that we found an effect due to exposure in the household — which includes the spouse's smoking— strongly suggests this possibility. Sandler's findings further support it (37). He found an increase in risk with the increasing number of household members who smoked, including the spouse. Intuition, together with these results, would seem to suggest that the most appropiate way to evaluate the effect of passive smoking

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would be through the use of a cumulative index of exposure. Although in theory this is desirable, the exigencies of collecting the information may proscribe it. People's perception of the smoking that goes on around them may vary from one circumstance to another. Whereas people may be able to provide more or less detailed and accurate information on the smoking of the spouse or other members of the family, they might not be as precise when it comes to the smoking of others or to the smoking that ocurrs in public places. Combining such information in a single index could result in the mixing of "good" quality information with some "bad" quality information, thus diminishing the probabilities of finding good estimators of the effect.

Lastly, an explanation for our negative findings may be attributable to the fact that smoking by the spouse is an exposure that is introduced late in life and may not be prolonged enough to produce an effect in and of itself. Such exposure, however, could become important in the presence of a previous exposure history (i.e. parental smoking) or, as explained above, in conjunction with exposure from other sources.

We found an increase in risk for lung cancer for those exposed to the smoke of others at home. The odds ratio associated with 150 person/years of exposure was estimated to be 1.86 (95% CL: 1.22 - 2.83). Only a few previous studies have included a measurement of exposure at home as a risk factor to be evaluated. In such studies, however, the measurement of exposure has been rudimentary, usually

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expressed as a dicothomy (yes/no exposure). We believe our measurement to be more complete given that it comprises a proxy for the intensity of the exposure (number of smokers in the household), as well as for its duration (number of years of cohabitation with smokers). It can also be regarded as a comprehensive measure, since it includes all household members for the subjects' residence history (the latter expanding for the most part of their adult lives). The collection of such extensive information, however, was not without its problems, as evidenced by the ocurrence of some missing values. We have explained the ways in which we approached such problem (by imputation of missing values under two different assumptions) and feel confident that our results have not been substantially affected by it.

The following are the results from other studies assessing the role of exposure to passive smoking at home.

Garfinkel et. al (30) classified the exposure to smoke at home according to how recent was the exposure. For those exposed at home in the last five years (yes/no exposure) an odds ratio was found for lung cancer of 1.22 (95% CL: 0.92 - 1.62). An even lower estimate was reported for exposure in the last 25 years (OR = 1.15, 95% CL : 0.89-1.49). These results were not statistically significant, as shown by the confidence intervals. A more refined measurement of exposure at home was also assessed by Garfinkel, but it was limited to spouse smoking. A significant linear association was found for exposure to the spouse smoking at home (no association was found for the smoking that occurs outside the home). Sandler et. al. (37) reported an elevated risk for those exposed at home. The odds ratios associated

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with 1, 2, and 3 or more smoking household members were 1.5, 2.3 and 2.8, respectively. Even though only the last figure was in itself statistically significant, the three figures together follow a statistically significant linear trend. Kabat and Wynder (34) found no association between exposure at home (yes/no exposure) and risk for lung cancer. Their estimates, however, are based on a study that included only 25 lung cancer patients.

In addition to the overall effect due to household exposure found in our data, there is one other finding that deserves special consideration. The effect of passive smoking in the household was found to be significantly larger for epidermoid/small cell histologic type than for adenocarcinoma/other cells histologic type (unadjusted odds ratios of 2.83 and 1.42, respectively). Controlling for confounding variables resulted in estimates, that although not significant, were nonetheless consistent with the above findings (adjusted OR = 2.32, and 1.86, respectively). As explained in the paragraphs above, only a few studies have classified their cases in regard to histologic diagnosis, and even fewer have included a large enough number of cases of each histologic type as to be able to examine specific associations. The notion that passive smoking may be more strongly associated with epidermoid tumors, therefore, comes mainly from studies on the effects of direct smoking. Although some of these studies have determined that all histologic types are related to smoking (see Chapter 1: "Smoking and Histologic Type of Lung Cancer"), most of them seem to agree that the strongest relationship is observed for epidermoid and small cell tumors. The suggestion that

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such findings hold as well for passive smoking provides support to the hypothesis that environmental smoke acts in a similar way to mainstream smoke and that stresses that the only differences between the two types of exposures are quantitative. The one other study that found a statistically significant higher risk for epidermoid type was that of Garfinkel's et. al. (30). They reported an odds ratio of 5.0 (95% CL: 1.43 - 20.18) associated with the husband's smoking at home. Another study reported similar result, although non significant. Dalager et. al.(33) reported an adjusted odds ratio of 2.88 (95% CL: 0.91-9.10) for epidermoid/small cell carcinomas, and an odds ratio of 1.02 (95% CL: .33-3.16) for adenocarcinoma.

The importance of passive smoking in the household must be put into perspective with regard to the amount of exposure necessary to observe an effect of the magnitude described. We have presented the estimates of effects associated with an exposure of 150 person/years. This is equivalent to having lived over a period of 30 years with five smokers, or with approximately 4 smokers for 37 years. It should be emphasized that such level of exposure is rather high and may be uncommon in the general population. In our study group, for instance, only 7.5% of the cases and 4.3% of the controls attained that or higher levels of exposure. Indeed, lower levels of exposure are much more common. For example, 25% of the cases and 20.5% of the controls reported exposures between 50 and 75 person/years (equivalent to having lived 25 years with 2 or 3 smokers). Such levels of exposure, however, carry risks that are more modest (OR for 50 person/years = 1.23, for 75 person years = 1.36).

The exposure to passive smoking that occurs in the workplace has been thought to be extensive enough to deserve consideration as a potential risk factor for lung cancer. Laboratory data has shown that the urinary cotinine levels of non-smokers working where smokers are present are significantly higher than those of non-smokers working with non-smokers (56). The epidemiologic evidence has not been yet reported. Garfinkel found odds ratios of 0.88 (95% CL: 0.66-1.18) and 0.93 (95% CL: 0.73 - 1.18) for smoke exposure at work in the last 5 and 25 years, respectively (yes/no exposure classification). Kabat and Wynder found a barely statistically significant effect due to exposure at work (yes/no exposure) for males, but not for females. In their study 18 of 25 cases reported to have been exposed to cigarette smoke at work compared to 11 of 25 controls (OR = 3.27). In our study the risk associated with exposure in the workplace was statistically indistinguishable from the null value (OR = .9740, 95% CL: 0.974 - 1.014; for 150 person/years of exposure). We also found that exposure in the workplace may not be as extensive as beleived. Nearly a third of our cases and controls reported no exposure at all in the workplace, and almost 50% reported exposures of less than 25 person/years. This distribution results in a small number of highly exposed individuals in which the effect, although more likely to develop, would also be more difficult to detect. Finally, accumulation of exposure in the household and exposure in the workplace in a single measurement of exposure (both were measured in the same units) provided non significant results. We believed, as mentioned earlier in this chapter, that this is the result of combining two measurements with two different degrees of sensitivity. Whereas smoking by members

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of the family may be closely correlated with the dose received by the passive smoker, the correlation between co-workers' smoking and the dose received by the passive smoker may not be as close.

No other study before ours had included the assessment of exposure to passive smoking in social circumstances. We lack, therefore, any point of reference by which to compare our unexpected results. We found a decrease in risk for lung cancer with increased exposure to an index created to reflect social passive smoking (OR = 0.639, 95% CL: 0.520 - 0.785). Given all the following — 1) the previous reports that have shown an association between exposure to passive smoking and lung cancer, 2) our own results that support such relationship (at least for one of the exposure variables), 3) the studies that have established the association between active smoking and the disease, and 4) the laboratory data that has confirmed the carcinogenic properties of tobacco smoke — the possibility of a contradictory effect of passive smoking on lung cancer risks seems unfounded.

In searching for an explanation of this result, we must consider two possibilities: 1) that the association found reflects a true relationship, and 2) that the results are product of data artifacts. A third possibility, the role of chance, has largely been discounted through the application of tests for which the statistical significance has been set at 0.05 (i.e. results such as the ones observed may have occured as a consequence of chance only in 5 out of 100 "trials").

If we assume first that the relationship found between social exposure to passive smoking (as measured) and lung cancer is true, we well might wonder what could have caused lung cancer patients to have been exposed to less social passive smoking than were the "healthy" controls. Any response along those lines would be merely speculative; but the following is one that has occurred to us. Suppose that the cases have indeed developed the disease as a consequence of exposure to passive smoking. According to our results, the "causal" exposure would be the one derived from smoking in the household; that is, from the only exposure for which we found significant results. It could then be argued that the exposure which occurs in the home cannot be avoided (or cannot be easily avoided), whereas exposure in social circumstances is something over which the individual has a certain degree of control. If those who are to develop lung cancer develop early respiratory symptoms (as is suggested by the fact that lung cancer is often preceeded by a poor respiratory function [67]), they may choose to avoid exposure to smoke in social circumstances, but find it harder to do so at home. Thus, exposure in the household would continue to permit the disease-generation process to be completed, while at the same time exposure from other sources would be diminished. Similarly, it could be proposed that, in addition to passive smoking in the household, there is an as yet unidentified risk factor responsible for a considerable proportion of the cases. Increasing exposure to such a risk factor among the cases, however, would also have to be associated with a decreasing exposure to social passive smoking. In this way the reverse association observed between social passive smoking and lung cancer would be real, but by no means

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would be causal.

A second possibility we have considered is that our results regarding social exposure are artifactual. What is most likely responsible for this is the use of an artificial index of exposure not previously validated through proper methodologic studies. Some factors which may have affected the quality of the information collected through such mechanisms as follows. First of all, the period of time covered by the questionnaire items is very lengthy. Eliciting good information on day-to-day events in the past requires a considerable effort of recollection. Particularly for the first years of life, a considerable recollection of the parent's or the family's social life, which are the main vehicle of exposure to environmental smoke, is required.

Secondly, the information as it was collected did not make any attempt to measure intensity of exposure, nor did it establish the relative importance of exposure during one activity as opposed to another. There is a real question, for instance, if visiting friends or relatives who smoke conveys the same degree of exposure as would be incurred by going to bars and restaurants. Thus, exposure for all activities was weighted equally.

Thirdly, the specific social activities specified to the interviewee in order to elicit a response — that is, those representative activities known to be conducive to exposure — were very limited (see Appendix A, page 173). For many study subjects the

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exposure might originate from very different sorts of social circumstances than those explicitly questioned. The failure specifically to mention those activities may conceivably have produced some underreporting.

Fourth, the use of two different units of time to measure frequency of exposure may also have confused the respondents. The less frequent exposures had to be reported according to the number of times a month the exposure occured, whereas the most frequent exposures had to be reported on a per/week basis.

Finally comprehension of the information being requested may have been impaired by the complex nature of the questions. Each inquiry demanded responses which simultaneously synthetized information on three different aspects of exposure (type of social activity, age of exposure, and frequency of exposure). Such questions, placed almost at the end of a one hour interview, may have been answered without the concentration necessary to provide altogether adequate responses.

We have not mention in the above list the use of surrogate respondents as a possible source of data artifacts. The reason is that we do not have any evidence to support that the estimates obtained for self-respondents are any different from those of surrogate respondents (This is a situation that is also true for all of our exposure variables, with one exception: the number of years smoked by the spouse). But given the common concern on that matter, we felt that it should be made explicit.

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Imperfections of the data collection tools alone, however, may not be sufficient to explain our results. It is the way in which such imperfections affected the response of cases vis-a-vis the response of controls that may provide additional understanding. Again, we can only speculate on this matter. Our results suggest that the cases may have underreported their exposure to social passive smoking. Such a problem is often mentioned in relation to studies in which the suspected exposure is socially undesirable, as is the case with drug or alcohol use. In the present instance, however, there is no such stigmatization attached to exposure. It is, after all, the smoking of others, and not the patient's own risk factor that is being implicated. Nevertheless, patients for whatever reason may have felt the need to minimize their exposure to anything that potentially they might have been able to avoid. (Overreporting of exposure by controls may also, in theory, have produced the results observed. In practice, however, there is no compelling reason to beleive that controls would benefit from such behaviour. As a consequence we have discounted overreporting as a possibility).

Throughout this document we have presented a summary of the information currently available on the relationship between lung cancer and passive smoking. In the first part we have reviewed the major epidemiologic studies on the subject, as well as some relevant laboratory data. The major portion of this document, however, has been devoted to the description of the methodology and the results of this, largest epidemiologic study so far conducted to examine the

afore-mentioned association. Both the strengths and weaknesses of the study have been indicated; but when these are put into a balance, we beleive to have gathered one of the best data sets to judge the extense of the purported relationship.

We were unable to confirm an association with the most commonly used measure of exposure (spouse smoking), but we did find an effect due to exposure to passive smoking in the household. These results, although only in partial agreement with those of other studies, are consistent with the existence of a small to moderate effect of passive smoking on lung cancer risks. We did not find an effect due to exposure to passive smoking in the workplace. We found, however, a decreased risk in lung cancer with increasing exposure to passive smoking in social circumstances. Possible reasons for such findings have been discussed above.

Our findings suggest that the previous studies may have overestimated the effect attributable to passive smoking. Such a possibility has been proposed by those who contend that a typical exposure to passive smoking is only equivalent to smoking actively less than one cigarette per day (which in itself conveys risks that are lower than the two-fold increase proposed for passive smoking). Methodologic problems that may have led to such overestimation of the effect have been pointed out in Chapter 1, as well as in this chapter.

As is well known to epidemiologists, the results of one study — or even a few studies— are seldom sufficient to answer all questions

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regarding the relationship between a putative risk factor and a disease. We believe the present study has contributed to a better understanding of the lung cancer risk involved in the exposure to passive smoking. Nevertheless, we think we are still far from knowing all the details necessary to establish a final judgment. Future studies will be necessary to take that step.

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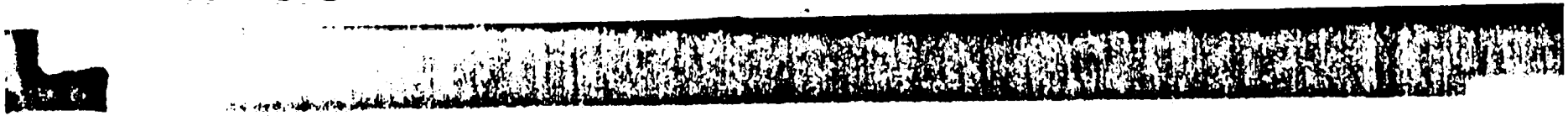

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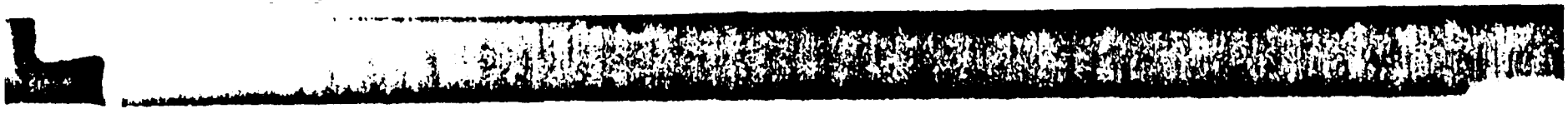

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APPENDIX A

ITEMS IN THE QUESTIONNAIRE SELECTED FOR ANALYSIS

CODE:

- (D) Sociodemographic variables
- (M) Matching variables
- (E) Outcome variables
- (X) Exposure variables
- (F) Confounding variables
- (C) Quality control variables

Time began /_/_/_/_/

	Record #	/1_/
(M)	ID #	/_/_/_/_/_/ 5
(C)	Interviewer	/_/_/_/ 7
(C)	Date of Interview	/_/_/_/_/_/_/_/ 13
(C)	Length of Interview (minutes)	/_/_/_/ 16
(D)	Residence distance	/_/_/_/_/ 20
(D)(C)	Sex 1. Male 2. Female	/_/ 21
(C)	Type of Interview 1. Individual 2. Surrogate: spouse 3. Surrogate: child 4. Surrogate: sibling or parent 5. Surrogate: other	/_/ 22

I'd like to begin by asking you a few general questions.

1. What is your date of birth? (D)(M) /_/_/_/_/_/_/ 28

2. In what country were you born? (CHECKING CODES) (D) /_/_/ 30 31

3. How many years of school have you completed? (CODE EXACT YEARS) (D) /_/_/ 32 33
   12 = High School
   16 = College Graduate
   18 = Masters degree
   20 = Doctorate

4. How tall are you? (CODE INCHES) /_/_/ 34 35
   5' = 60"
   6' = 72"

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Reward # /_/

ID # /_/_/_/_/

SMOKING HISTORY

FORMER SMOKERS ONLY
(cases and controls)
NON-SMOKERS SKIP TO PASSIVE
SMOKING SECTION

Now I'd like to ask you a few questions about your smoking history.

21. How old were you when you first started smoking cigarettes on a regular basis, that is, at least one cigarette a day for at least a year? (6) — 6 /_/_/ 7

22. How old were you when you stopped smoking cigarettes on a regular basis? (6) — 8 /_/_/ 9

23. During these years did you ever stop smoking for more than one year? (6) — 10 /_/

1. Yes --- A. During how many of these years were you not
2. No smoking? (6) — 11 /_/_/ 12

24. On an average, how many cigarettes per day did you usually smoke? (6) — 13 /_/_/ 14

(1 pack = 20 cigarettes)

25. Did you usually smoke filter, non-filter cigarettes, or both? (6) — 15 /_/

1. Filter
2. Non-Filter
3. Both

26. Did you inhale the smoke? — 16 /_/

1. Yes
2. No (6)

ID # [ ][ ][ ][ ]

OCCUPATIONAL HISTORY

I'd like some information about each of the jobs or occupations you have had, including any jobs you may have held while in the armed services. You don't need to tell me about jobs that lasted less than a year or jobs you had while still in school. Let's start with your most recent job.

What was your job title?	What were your most important activities or duties	Name and location of business	What did this business do?	What years did you work there?
	74 /_/_/_/ 75		77 /_/_/_/ 79	From 80 /_/_/ to 82 /_/_/ 83 (5) (6)
	94 /_/_/_/ 95		97 /_/_/_/ 99	(5) (6) 100 /_/_/ to 102 /_/_/ 103
	114 /_/_/_/ 116		117 /_/_/_/ 119	(5) (6) 120 /_/_/ to 122 /_/_/ 123
	134 /_/_/_/ 136		137 /_/_/_/ 139	(5) (6) 140 /_/_/ to 142 /_/_/ 143
	154 /_/_/_/ 156		157 /_/_/_/ 159	(5) (6) 160 /_/_/ to 162 /_/_/ 163
	174 /_/_/_/ 176		177 /_/_/_/ 179	(5) (6) 180 /_/_/ to 182 /_/_/ 183
	194 /_/_/_/ 196		197 /_/_/_/ 199	(5) (6) 200 /_/_/ to 202 /_/_/ 203
	214 /_/_/_/ 216		217 /_/_/_/ 219	(5) (6) 220 /_/_/ to 222 /_/_/ 223
	234 /_/_/_/ 236		237 /_/_/_/ 239	(5) (6) 240 /_/_/ to 242 /_/_/ 243
	254 /_/_/_/ 256		257 /_/_/_/ 259	(5) (6) 260 /_/_/ to 262 /_/_/ 263
	274 /_/_/_/ 276		277 /_/_/_/ 279	(5) (6) 280 /_/_/ to 282 /_/_/ 283
	294 /_/_/_/ 296		297 /_/_/_/ 299	(5) (6) 300 /_/_/ to 302 /_/_/ 303

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ID # [ ][ ][ ]

IF YES: Did the building have a (1) basement or (2) crawlspace	Did any of those houses have a gas cooking range? (1) Yes (2) No	Were any of those houses heated by kerosene? (1) Yes (2) No	Were any of those houses heated with a coal or wood stove? (1) Yes (2) No	Did any of those houses have a kitchen fan that either blew cooking smoke or odors (1) outside or (2) inside?	Were any of those residences a mobile home or trailer (1) Yes (2) No
/_/ 13	/_/ 14 $	/_/ 17 $	/_/ 18 $	/_/ 19	/_/ 20
/_/ 30	/_/ 31 $	/_/ 34 $	/_/ 35 $	/_/ 36	/_/ 37
/_/ 46	/_/ 47 $	/_/ 50 $	/_/ 51 $	/_/ 52	/_/ 53
/_/ 62	/_/ 63 $	/_/ 66 $	/_/ 67 $	/_/ 68	/_/ 69
/_/ 78	/_/ 79 $	/_/ 82 $	/_/ 83 $	/_/ 84	/_/ 85
/_/ 94	/_/ 95 $	/_/ 98 $	/_/ 99 $	/_/ 100	/_/ 101
/_/ 103	/_/ 104 $	/_/ 107 $	/_/ 108 $	/_/ 109	/_/ 110
/_/ 119	/_/ 121 $	/_/ 123 $	/_/ 123 $	/_/ 124	/_/ 125
/_/ 135	/_/ 136 $	/_/ 137 $	/_/ 138 $	/_/ 139	/_/ 140
/_/ 150	/_/ 151 $	/_/ 153 $	/_/ 153 $	/_/ 154	/_/ 155
/_/ 165	/_/ 166 $	/_/ 167 $	/_/ 168 $	/_/ 169	/_/ 170
/_/ 180	/_/ 181 $	/_/ 182 $	/_/ 183 $	/_/ 184	/_/ 185

ID # [ ][ ][ ]

PASSIVE SMOKING

37. Have you ever smoked any of the following?

		1. Yes 2. No	Age 1st Started	Current Smoker 1. Yes 2. No	Age Stopped	# Smoked per day	Inhale 1. Yes 2. No
$	Cigars	17 /_/	18 /_/_/ 19	/_/ 20	21 /_/_/ 22	23 /_/_/ 24	/_/ 25
$	Pipes	26 /_/	27 /_/_/ 28	/_/ 29	30 /_/_/ 31	32 /_/_/ 33	/_/ 34
$	Marijuana	35 /_/	36 /_/_/ 37	/_/ 38	39 /_/_/ 40	41 /_/_/ 42	/_/ 43

		1st	2nd	3rd	5th
38.	Are you currently: (1) single (never married) (2) married (3) widowed (4) divorced (5) separated	/_/ 44			
39.	How many times have you been married?	/_/ 45			
40.	How many years were you married and living together with your (1st, 2nd, 3rd, 4th) husband/wife?	/_/_/ 46 47	/_/_/ 48 49	/_/_/ 50 51	/_/_/ 52 53
41.	Did your (1st, 2nd, 3rd, 4th) husband/wife smoke during the time that you were married and living together? (1) YES --- A. How many cigarettes per day did he/she smoke? (2) NO B. How many years did he/she smoke when you were married and living together?	/_/ 54	/_/ 55	/_/ 56	/_/ 57
		/_/_/ 58 59	/_/_/ 60 61	/_/_/ 62 63	/_/_/ 64 65
		/_/_/ 66 67	/_/_/ 68 69	/_/_/ 70 71	/_/_/ 72 73

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ID # [ ][ ][ ][ ]

SOCIAL HISTORY

Now, I'm going to ask you about the amount of time you spent on some activities during certain periods of your life. I'd like you to answer using the responses on this card.

HAND CARD #1

ACTIVITIES	RESPONSES
1. Visiting in house of friends and relatives who smoked	0. Never
2. In bars or restaurants	1. 4 times a month
3. In any other activity that you recall being among people who smoked, such as bowling, playing bingo, in fraternal clubs and organizations, etc.	2. 1-3 times a month
	3. 1-3 times a week
	4. 4-7 times a week

Worksheet:

Fill Responses in the boxes, add, and note total.

Activities				Age		
1. ☐	2. ☐	3. ☐		1-10	ⓐ	186 /_/_/ 187
1. ☐	2. ☐	3. ☐		11-20	ⓐ	188 /_/_/ 189
1. ☐	2. ☐	3. ☐		21-30	ⓐ	190 /_/_/ 191
1. ☐	2. ☐	3. ☐		31-40	ⓐ	192 /_/_/ 193
1. ☐	2. ☐	3. ☐		41-50	ⓐ	194 /_/_/ 195
1. ☐	2. ☐	3. ☐		51-60	ⓐ	196 /_/_/ 197
1. ☐	2. ☐	3. ☐		61-70	ⓐ	198 /_/_/ 199
1. ☐	2. ☐	3. ☐		71-80	ⓐ	200 /_/_/ 201

ID # [ ][ ][ ] 1

32. Have you ever worked with dyes or pigments? /_/ 219

(1) YES (2) NO ③

33. Have you ever worked with substances which were very hot? /_/ 220

(1) YES (2) NO ③

34. Did any of the hobbies you have had ever involve any of the following?

(1) YES (2) NO

A. Woodworking ③ /_/ 221

B. Painting (house or furniture) /_/ 222

C. Glue /_/ 223

D. Garden Spray /_/ 224

35. Did any of the hobbies that you've had involve working with any toxic substances? ③ /_/ 225

(1) YES ---- Specify _____

(2) NO _____

_____

_____

- -

I have a few final questions.

36. What is your religious affiliation, if any? ⑧ /_/ 226

(1) Catholic
(2) Protestant
(3) Jewish
(4) Other _____
(5) None

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ID # ☐☐☐☐

HOME CARD #2

37. Which of these categories best describes your total household income last year before taxes? (E) /_/_/ 227 228

01-A	Under $4,000	06-F	16,000 - 18,999
02-B	4,000 - 6,999	07-G	19,000 - 21,999
03-C	7,000 - 9,999	08-H	22,000 - 24,999
04-D	10,000 - 12,999	09-I	25,000 - 29,999
05-E	13,000 - 15,999	10-J	Over $30,000

WOMEN ONLY

38. Did you ever take oral contraceptives? /_/ 229

(1) Yes ——— A. How many years did you take them? 230 /_/_/ 231
(2) No

IF OBSERVATION: Ethnic Category (E) /_/ 232

(1) White
(2) Black
(3) Oriental
(4) Other
(9) Unknown

Is there anything else about your background or past history that you think is important to this study, even if I didn't specifically ask about it?

_____

_____

_____

_____

Time ended /_/_/_/_/

ID # ☐☐☐☐

CHEMICAL EXPOSURES

Now, I'd like to ask you about substances you may have been exposed to. I'm going to read you a list of materials, many of which may sound unfamiliar to you. But if you have had a job, military duty or hobby that involved any of these substances, you will probably recognize the name when I read it. Have you ever been exposed to:

(1) YES (2) NO IF YES: PLEASE EXPLAIN

A.	Asbestos	(E)	/_/ 202
B.	Asphalt	(E)	/_/ 203
C.	Arsenic	(E)	/_/ 204
D.	Beryllium	(E)	/_/ 205
E.	Chromium or Chromates	(E)	/_/ 206
F.	Formaldehyde	(E)	/_/ 207
G.	Chloromethyl ether	(E)	/_/ 208
H.	Soy dust	(E)	/_/ 209
I.	Herbicides (such as Agent Orange)	(E)	/_/ 210
J.	Nickel	(E)	/_/ 211
K.	Mustard gas	(E)	/_/ 212
L.	Plastics	(E)	/_/ 213
M.	Polyvinyl chloride	(E)	/_/ 214
N.	Any type of radiation	(E)	/_/ 215
O.	Uranium	(E)	/_/ 216
P.	Sand	(E)	/_/ 217
Q.	Sprays for orchards or vineyards which contain arsenic	(E)	/_/ 218

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Kabat, G.C., "Epidemiologic Studies of the Relationship Between Passive Smoking and Lung Cancer," Toxicology Forum, 1990 Annual Winter Meeting (transcript): 187-199, 1990.

This multicenter case-control study currently in progress in the United States (90 cases and 247 controls recruited to date) intends to investigate "tobacco-related diseases." All cases were histologically confirmed; controls were hospitalized persons, matched to cases by age, sex, race, hospital and date of interview. Apparently no proxy respondents were used. Questions concerned ETS "exposure" in utero, during childhood, during adulthood, at the workplace, in transportation and in social settings. The potential confounders of demography, occupation, alcohol consumption, medical history, diet, and "other factors" were included.

For ETS exposure during adulthood in the home, an RR of 1.20 (95% CI 0.54-2.68) was reported for males; for females, the reported RR was 0.90 (95% CI 0.46-1.76). For workplace exposure, RRs of 0.98 (95% CI 0.46-2.10) and 1.00 (95% CI 0.49-2.06) were reported for males and females, respectively. The RRs for childhood exposure varied substantially between the sexes: 0.73 (95% CI 0.34-1.59) for males and 1.68 (95% CI 0.86-3.27) for females. None of the reported RRs was statistically significant.

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JUN 25 1990

TOXICOLOGY FORUM

1990 Annual Winter Meeting

February 19-21, 1990
L'Enfant Plaza Hotel
Washington, D.C.

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1990 Annual Winter Toxicology Forum

L'Enfant Plaza Hotel
Washington, D.C.

February 19-21, 1990

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DR. KABAT: Thank you.

The problem of passive smoking and lung cancer has provoked a good deal of debate both on a scientific and on a public policy level. Do the studies that purport to show an association of exposure to environmental tobacco smoke (ETS) and lung cancer occurring in lifetime nonsmokers provide adequate evidence to resolve the issue? As Nancy Haley has just shown, she and her colleagues are very good at measuring recent exposure to ETS using cotinine measured in saliva, serum, and urine. Unfortunately, these biomarkers are not helpful for assessing exposure over the several decades relevant to the induction of lung cancer. Given the lack of a biomarker for long-term exposure to ETS, epidemiologic studies have had to rely on self-reports or proxy-reports of ETS exposure.

I propose to raise what I consider to be some of the key aspects of the roughly 15 epidemiologic studies of the issue of ETS and lung cancer and to point out certain areas that require further study. I will briefly refer to our own study which is still in progress at the American Health Foundation. Finally, I will suggest a possible direction for further study of this issue.

EPIDEMIOLOGIC

Table 1 lists studies examining the lung cancer risk of non-smoking wives of smoking husbands compared to the non-smoking wives of non-smoking husbands. One notes that the greatest magnitude of the overall relative risk (RR) is 2.1. After the Trichopoulos and Correa studies, the highest RR is 1.65 (Lam et al.). The national Research Council's committee on passive smoking carried our a meta-analysis of the existing studies in 1986 and came up with an overall RR of 1.34 (95% confidence interval: 1.18-1.53) (1).

In four out of the fifteen studies listed, the overall RR is statistically significant. When one examines the data by level of exposure, i.e., number of cigarettes per day smoked by the husband stratified into two or more levels, 8 of the 15 studies show evidence of a dose-response relationship.

HISTOLOGY

When we look at the effect of ETS exposure by histologic type, we see an interesting discrepancy (Table 2). Dalager et al. (2) and Pershagen et al. (3) show roughly comparably elevated odds ratios (OR) for squamous cell and small cell carcinomas combines, but not for adenocarcinoma. In contrast, Lam et al. (4) obtained a significant effect for adenocarinoma but not for squamous cell carcinoma.

The results of Hirayama's study (5) presumably agree on this point with those of Lam et al., since the majority of his lung cancer cases were apparently adenocarcinoma. Trichopoulos et al. results (6) presumably weigh in on the side of Dalager et al. and Pershagen et al., since Trichopoulos excluded adenocarinoma and terminal bronchial carcinoma from their series.

Since adenocarinoma occurs more commonly in never smokers than in smokers and generally more commonly in women than in men (7), one would expect that if ETS exposure is an appreciable risk factor for lung cancer, it is associated with adenocarcinoma, as well as possibly with other types. The inconsistency in the results to date regarding histology indicates that this is one area that merits further study.

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ASSESSMENT OF DISEASE STATUS

Misclassification on disease status occurs when diagnoses other than primary carcinoma of the lung are included in the case series or when a primary cancer of the lung is included among the controls due to its having gone undetected. Garfinkel et al. reported that of 283 women listed as having lung cancer in hospital records but with no mention of their having smoked, 36 (12.7%) turned out to have diagnoses other than lung cancer when the histology was reviewed by one of the authors (8).

In studies in which histologic verification of lung cancer is a criterion for inclusion in the study, misclassification should be minimal. However, some of the studies listed in Table 1 were lacking this for all cases.

It should also be mentioned that even when lung cancer is histologically verified, it is possible that some cases judged to be primary cancer of the lung are actually secondary to a cancer of another site that has gone undetected.

ASSESSMENT OF EXPOSURE STATUS

This is a greater problem than assessment of disease status, and for some investigators it is the key problem of epidemiologic studies of ETS and lung cancer (9,10).

Misclassification of exposure status can occur in a number of ways. First, subjects who have smoked for some period of their life can be erroneously included in a study of never smokers. Second, subjects may under-report (minimize) or over-report (inflate) their ETS exposure, or this may be done by proxies. A third type of misclassification can occur when some indirect measure (such as whether the subject is married to a smoker or how much the spouse smokes) is used as an indicator of ETS exposure. The effect of misclassification on the estimate of the RR depends on whether the misclassification is random or differential (that is systematic). Random misclassification will bias the estimate of the RR toward the null, thus making an effect, if there is one, more difficult to detect. If misclassification on exposure differs between cases and controls, the estimate of the RR can be biased either upwards or downwards depending on the direction of the bias (11).

Misclassification of active smokers as never smokers.

Garfinkel and co-workers found that among lung cancer cases identified as "nonsmokers" or lacking any mention of smoking in the hospital record, 40% were revealed to have smoked upon reinterview (8). Although a detailed personal interview yields more accurate smoking histories than reliance on hospital charts, it is still likely that, even when subjects are directly interviewed and more so when various proxies are used, some misclassification of smokers as nonsmokers occurs.

Lee has argued that random misclassification of smokers as non-smokers coupled with a tendency of smokers to marry smokers could account for the observed association of a spouse's smoking and increased lung cancer risk in non-smoking spouses (9). Assuming a 5% misclassification of smoking subjects, a RR of 20 for active smoking, no true effect of passive smoking, and a between-spouse smoking concordance of 3.45, Lee demonstrates the effects of such a bias. These include an apparent effect of passive smoking (RR = 1.75) and the creation of a large proportion of true smokers among the self-reported non-smokers with lung cancer.

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Misclassification of self-reported ETS exposure.

A study by Pron et al. (12) suggests that misclassification of self-reported ETS exposure may be extensive. They examined the reliability of responses in 117 control subjects who had participated in a study of passive smoking and who were reinterviewed on average six months later. Responses to an initial question about exposure to ETS (yes/no) were more reliable for exposure at home than at work (Table 3). Reproducibility of questions concerning exposure to a spouse's smoke (yes/no) was high for both sexes, with the reliability being generally lower for other family members. Quantitative measures of ETS exposure, i.e., number and duration of exposures, were generally less reliable than qualitative (or dichotomous) measures. In general, non-smokers gave more reliable information on all parameters of ETS exposure than smokers.

Unfortunately the study by Pron et al, did not examine the reliability of responses among cases as well as among controls. In case-control studies particularly one must be concerned that the case's reporting of exposure may be influenced by his diagnosis. In a study of lung cancer occurring in non-smokers, this could take the form of cases probing past exposures more intensively than controls and over-reporting exposures to ETS, since some cases may feel compelled to find an explanation for their disease. On the other hand, it is also possible that cases might minimize their exposures out of an unwillingness to blame a spouse.

Misclassification due to use the spouse's smoking habits.

Using the presence of a smoking spouse as an indicator of ETS exposure can lead to serious misclassification of exposure. Based on a survey of nearly 38,000 never- and ex-smokers, Friedman et al. (13) reported that the sensitivity and specificity of using the presence of a smoking spouse as a predictor of actual ETS exposure were quire poor. Thirty-nine percent of men and 47% of women married to smokers reported zero hours of exposure at home. Conversely, 49% of men and 41% of women married to non-smokers reported some ETS exposure.

CONFOUNDING

Confounding is another major problem area for the evaluation of epidemiologic studies of ETS and lung cancer and one that has received relatively little attention.

Several studies suggest that a variety of factors could act as confounders of an ETS-lung cancer association. Friedman (13) found that age bore a strong negative relationship to reported ETS exposure. Hours per week of ETS exposure were associated with alcohol consumption, marijuana use, being currently unmarried, and, in a U-shaped fashion, with "no college education."

Koo, Ho, and Rylander (14) examined a wide variety of behaviors of the non-smoking wives of smoking and non-smoking husbands in Hong Kong. They concluded that in general wives with husbands who had never smoked had healthier lifestyles than wives with smoking husbands. Specifically, the former were of higher socioeconomic status, were more conscientious housewives, ate better diets, and had higher indices of family cohesiveness as well as better health status.

A third study, by Sidney et al. (15) reported that dietary B-carotene intake was significantly lower in non-smokers exposed to passive smoke at home than in non-smokers who were not exposed, after adjustment for ag e, sex, race, education status, body weight, and alcohol intake.

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They concluded that dietary B-carotene intake was a potential confounder of the relationship between ETS and lung cancer.

Other potential confounders included: occupation, domestic radon exposure, a history of exposure to therapeutic x-rays, and keeping pet birds in the home. This last is raised by a recent study from the Netherlands which found that the odds ratio for lung cancer among people who kept pet birds in their home was 6.7 (95% confidence interval 2.2-20.0) after adjustment for active smoking and vitamin C intake (16). This study did not assess ETS exposure among the subjects.

THE AMERICAN HEALTH FOUNDATION STUDY

Since 1983, a study of ETS and lung cancer in never smokers has been in progress at the American Health Foundation. All lung cancer cases interviewed in the context of a large, multi-center study of tobacco-related diseases who report never having smoked more than one cigarette per day for a year are given a detailed ETS questionnaire.

For each case, 2-3 hospitalized controls who have diagnoses not known to be associated with tobacco use and who are also lifetime non-smokers are interviewed. Controls are matched to cases on age (+/- 5 years), sex, race, hospital, and date of interview (within 3 months).

The items in the questionnaire include exposure in utero; in childhood (specific family members who smoked, years of exposure and average number of hours of exposure per day, and a subjective rating of the intensity of exposure), in adulthood at home (specific family members who smoke(d), number of cpd smoked by each, years of exposure, number of hours per day, subjective rating of exposure, and where a spouse smoked, whether he or she smoked in the bedroom); in the workplace (number of hours per week, years of exposure, number of smokers within ten feet of subject, rating of exposure) for up to four different jobs; and in various forms of transportation and in social situations.

In addition to ETS questions, information is obtained on demographic factors, occupation, alcohol consumption, medical history, diet, and other factors. To date, this study has accrued a total of 90 lung cancer cases and 247 matched controls. We plan to continue recruiting subjects for the study in order to reach a sample size of 150 cases. Table 4 gives a breakdown of the histology of lung cancer by sex.

Preliminary analyses of the data do not indicate any striking ETS exposure differences between cases and controls. Tables 5 and 6 give crude odds ratios and confidence intervals for overall exposure in childhood, adulthood at home, and in the workplace, in males and females, respectively. With the possible exception of exposure in childhood and among women, there is little suggestion of excess risk due to ETS. A fuller analysis of these data, including adjustment for covariates, is in progress.

CONCLUSION

Epidemiologic studies of ETS and lung cancer generally suffer from small sample size. Given the small magnitude of the observed RR associated with passive smoking and the problems associated with multiple histologic types bias, misclassification, and confounding, increasing the sample size is one way to attempt to answer the ETS-lung cancer question with greater certainty. A case-control study of 10,000 lung cancer cases (7,500 males and 2,500 females) could be expected to

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yield approximately 150 male and 250 female never smokers, based on estimates of the frequency of lung cancer among never smokers (2% for males and 10% for females [7]). Table 7 shows the sample sizes necessary in each group (assuming equal numbers of cases and controls) to detect RRs between 1.25 and 2.00, with a one-tailed alpha of 5% and 80% power, given various proportions of exposed controls.

While it is highly unlikely that such a study would be funded solely to assess the effects of ETS exposure, the study could be designed to make an important contribution to the radon-lung cancer issue as well. Specifically, studies of domestic radon exposure have also suffered from small sample sizes and have produced variable and unstable estimates of the risk of radon exposure in never smokers. In addition, there is a need to better assess the interactive effects of active smoking and radon exposure. Since ETS and radon exposure are both risk factors for lung cancer, and since one may confound, or interact with, the other, a large study designed to measure both factors as reliably as possible would have considerable scientific merit.

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Table 1

Epidemiologic Studies

Prospective Studies	*Relative Risk*	*95% C.I.*
Hirayama (1981)	1.63	1.25 - 2.11
Garfinkel (1981)	1.18	0.90 - 1.54
Case-Control Studies		
Trichopoulos, et al. (1981)	2.1	1.18 - 3.78
Chan & Fung (1982)	0.75	0.44 - 1.30
Correa, et al. (1983)	2.03	0.83 - 5.03
Koo, et al. (1983)	1.54	0.90 - 2.64
Kabat & Wynder (1984)	0.79	0.26 - 2.43
Wu, et al. (1985)	1.2	0.6 - 2.5
Garfinkel, et al. (1985)	1.12	0.74 - 1.69
Lee, et al. (1985)	1.03	0.41 - 2.47
Akiba, et al. (1986)	1.48	0.88 - 2.50
Dalager, et al. (1986)	1.5	0.8 - 2.8
Pershagen, et al. (1987)	1.28	0.75 - 2.16
Lam, et al. (1987)	1.65	1.16 - 2.35
Koo, et al. (1987)	1.55	0.94 - 3.08

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Cell Type Related to Spouse's Smoking

Study	*Histologic Type*	*N*	*Odds Ratio*	*95% C. I.*
Dalager et al. (1986)	Adenocarcinoma	16	1.02*	0.33 – 3.16
	Squamous & Small Cell Ca.	14	2.88*	0.91 – 9.10
	Other	18	1.31*	0.48 – 3.57
Pershagen et al. (1987)	Squamous or Small Cell Ca.	20	3.3	1.1 – 11.4
	Other	47	0.8	0.4 – 1.5
Lam et al. (1987)	Adenocarcinoma	131	2.12	1.32 – 3.39
	Squamous Cell Ca.	27	0.85	0.35 – 2.06
	Small Cell Ca.	8	3.00	0.53 – 16.9

*Adjusted for gender, age, and study area.

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Table 3

Reproducibility of ETS Exposure Data

Question	*Kappa value*
Ever lived with regular smoker?	0.66
Ever exposed to smoke at work?	0.46
No. of resident smokers?	0.55
No. of job sites reported?	0.37
Duration of residential exposure?	0.45

Source: Pron et al., 1988

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Histology of Lung Cancer Among Never-Smokers

	Males		*Females*	
	N	(%)	N	(%)
Squamous & Small Cell Ca.	5	(13.5)	10	(18.9)
Adenoca.	25	(67.6)	26	(49.1)
Large Cell Ca.	5	(13.5)	6	(11.3)
BAC	1	(2.7)	7	(13.2)
Other	1	(2.7)	4	(7.5)
	37		53	

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Table 5

American Health Foundation Study

Males

		Cases	Controls	OR	95% C.I.
Exposed in Childhood:					
	No	15	36	1.00	-----
	Yes	21	69	0.73	0.34 - 1.59
Exposed in Adulthood-at home:					
	No	23	68	1.00	-----
	Yes	13	32	1.20	0.54 - 2.68
Exposed at Work (ever):					
	No	16	45	1.00	-----
	Yes	21	60	0.98	0.46 - 2.10

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Table 6

American Health Foundation Study

Females

		Cases	Controls	OR	95% C.I.
Exposed in Childhood:					
	No	17	61	1.00	-----
	Yes	36	77	1.68	0.86 - 3.27
Exposed in Adulthood-at home:					
	No	18	45	1.00	-----
	Yes	35	97	0.90	0.46 - 1.76
Exposed at Work (ever):					
	No	17	43	1.00	-----
	Yes	27	68	1.00	0.49 - 2.06

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Table 7

Power Calculation

Odds Ratio To Detect	Percent Controls Exposed		
	20%	40%	60%
1.25	1616	1124	1172
1.50	419	303	329
1.75	214	161	179
2.00	134	104	119

$\alpha = .05$ (1-tailed) 1-B=.80 R = 1

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Kalandidi, A., Katsouyanni, K., Voropoulou, N., Bastas, G., Saracci, R. and Trichopoulos, D., "Passive Smoking and Diet in the Etiology of Lung Cancer Among Non-Smokers," Cancer Causes and Control 1: 15-21, 1990.

This case-control study "was undertaken to examine the role of diet and passive smoking in the causation of lung cancer in non-smokers." Cases (160 in total) were identified from 6 major hospitals in Athens; controls (women hospitalized with orthopedic conditions) were chosen from these hospitals or from a nearby orthopedic hospital. Questions included lifetime exposure to "passive smoking" from husbands, from other household members, and at work, and average frequency of consumption of 47 foods or beverages. Air pollution exposure was controlled for in the analysis on the basis of residential and employment addresses. Of the total cases and controls, 91 and 120 were classified as lifetime nonsmokers (<100 cigarettes in their lifetime); 48% of cases were diagnosed histologically and 38% cytologically.

The authors reported a RR for marriage to a smoker of 1.92 (95% CI 1.02-3.59). They also write "[t]here was no evidence of any effect from exposure to smoking of other household members." For workplace exposure, the RR "between extreme quartiles" was 1.08 (95% CI 0.24-4.87).

The authors report a protective effect for fruit consumption (RRs in the range of 0.2), but not for vegetables. The authors acknowledge that low fruit consumption and exposure to husband's cigarette smoking could acct as confounders.

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Cancer Causes and Control, 1, 15 – 21

Passive smoking and diet in the etiology of lung cancer among non-smokers

Anna Kalandidi, Klea Katsouyanni, Nelly Voropoulou, George Bastas, Rodolfo Saracci, and Dimitrios Trichopoulos

(Received 4 April 1990; received in revised form 1 May 1990; accepted 3 May 1990)

A case-control study was undertaken in Athens to explore the role of passive smoking and diet in the causation of lung cancer, by histologic type, in non-smoking women. Among 160 women with lung cancer admitted to one of seven major hospitals in Greater Athens between 1987 and 1989, 154 were interviewed in person; of those interviewed, 91 were life-long non-smokers. Among 160 identified controls with fractures or other orthopedic conditions, 145 were interviewed in person; of those interviewed, 120 were life-long non-smokers. Marriage to a non-smoking woman to a smoker was associated with a relative risk for lung cancer of 2.1 (95% confidence interval [CI] 1.1 – 4.1); number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data collected through a semi-quantitative food-frequency questionnaire indicated that high consumption of fruits was inversely related to the risk of lung cancer (the relative risk between extreme quartiles was 0.27 (CI 0.10 – 0.74)). Neither vegetables nor any other food group had an additional protective effect; furthermore, the apparent protective effect of vegetables was not due to carotenoid vitamin A content and was only partly explained in terms of vitamin C. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma.

Key words: Lung cancer, passive smoking, diet, air pollution, vitamin A, vitamin C, carotene.

Introduction

The association between involuntary exposure to tobacco smoke and lung cancer was first reported in 1981;[1,2] by the end of 1989 more than 20 epidemiologic studies had examined this issue.[3-10] In about one-third of these studies there were statistically significant positive associations between passive smoking and lung cancer risk, whereas in another third there were positive but statistically non-significant relationships, and in the remaining third the associations were minimal or non-existent. Overall the association between passive smoking and lung cancer is highly significant and, for practical purposes, chance can be excluded as a possible explanation. On the basis of biologic plausibility and epidemiologic evidence, causality appears the most likely explanation of the empirical association, but this view has not been uniformly accepted. It has been suggested that the association may reflect misclassification of ex-smokers among non-smokers (ex-smokers are at increased risk of lung cancer and are more likely to be married to smokers relative to life-long non-smokers), or to confounding effect(s) of unspecified factor(s). One such factor could be nutrition (*e.g.*, nutrition poor in carotenoid sources of vitamin A) since passive smokers may be less health-conscious than non-exposed persons. The present study was undertaken to examine the role of diet and passive smoking in the causation of lung cancer in non-smokers, by histologic type. Special emphasis was given to the exclusion of ex-smokers from any analysis concerning lifelong non-smokers.

Materials and methods

All women hospitalized during an 18-month period (1987 – 89) in seven hospitals of the Greater Athens area

Drs Kalandidi, Katsouyanni, Voropoulou, and Bastas are in the Department of Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece. Dr Saracci is at the International Agency for Research on Cancer, Lyon, France. Dr Trichopoulos is in the Department of Epidemiology, Harvard School of Public Health. Reprint requests should be sent to Dr Trichopoulos at 655 Huntington Avenue, Boston, MA 02115, USA.
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with a definite diagnosis of lung cancer formed the case series. The hospitals included all three cancer hospitals in this area, the only hospital for chest diseases in Athens, and the three largest university general hospitals. Women were included when there was a positive histologic or cytologic examination or when bronchoscopy was considered diagnostic of primary bronchogenic carcinoma. A total of 160 cases were identified. Controls were 160 women hospitalized in the orthopedic departments of the same hospitals or the nearby hospital for orthopedic disorders, to which most accident cases from Greater Athens and the surrounding area are admitted. Controls were randomly selected from those admitted within a week after the identification of a corresponding case and had to be 35 years of age or over. Among the control women, 102 had fractures and the remaining 58 had other traumatic or orthopedic conditions.

All cases and controls were interviewed in person in the hospital wards, as soon as a definite diagnosis was established, by one of five interviewers who each interviewed the same proportion of cases and controls. There were no refusals among cases but six were too ill to be interviewed. Among controls, 12 were in a condition that did not permit interview, and three refused to participate. In the interviews, patients were asked to indicate in detail their lifelong smoking histories, their exposure to passive smoking—from their husbands, from other household members and at work—as well as a number of other demographic, socioeconomic, and medical characteristics. Subjects were also asked to estimate the average frequency of consumption (per month, per week, or per day), before the onset of the present disease, of 47 food items or beverage categories. These items were selected from an extensive list of 120 items, using the criterion that the selected items should cover, collectively, more than 80% of the intake of each of the energy-generating nutrients as well as of vitamin A. This criterion was established on information from control groups in a number of case-control studies undertaken in Athens to explore the role of diet in the causation of cancer at various sites.[11]

Lifetime exposure to air pollution was controlled in the analysis on the basis of information about the lifelong residential and employment addresses of all subjects. The areas of residence and work were divided into five categories according to their estimated outdoor air-pollution levels. For the Greater Athens area, air-pollution levels by borough were calculated on the basis of the mean yearly measurements (1983 – 85) of smoke and NO_2, as recorded in 14 monitoring stations dispersed throughout the area. A line for zero air pollution was drawn at the highest points of the surrounding mountains. For each borough, the calculated air-pollution level was the average of the measurements of the three nearest stations, or the two nearest and the zero air-pollution line, weighted by the inverse of the distance from the borough's center to the measurement points. Boroughs were then divided into four categories, category 4 being the most polluted with daily smoke values frequently in excess of 400 $\mu g/m^3$ and category 1 being the less polluted with daily peak-smoke values rarely exceeding 100 $\mu g/m^3$. Past residences in rural or semi-urban areas (population less than 10,000) were considered as category 0, whereas past residences in other cities of Greece were classified in categories 1 or 2 according to the recorded or presumed levels of air pollution. Finally, for every individual, a time-weighted sum was calculated assuming 40 hours per week working time for individuals working outside the home. For housewives, their home residence formed the only basis for estimating their air-pollution exposure. When all subjects had their air-pollution exposure assessed, they were distributed into four groups based on the marginal quartiles of the air pollution index distribution. Since it is possible that the hospital catchment areas are larger for cancer patients than for patients with minor fractures and traumas, the possible air-pollution associations were taken into account only in order to control for possible confounding (generated by either genuine causal effects or through selection forces), and not for assessment of causality.

Among the 154 cases, 91 had been life-long non-smokers (less than 100 cigarettes in their lifetime); among them, 44 were diagnosed histologically (48%), 34 cytologically (38%), and 13 (14%) through bronchoscopy. Among the 145 controls, 120 had been life-long non-smokers. The analysis was confined to life-long non-smokers.

Three sources of passive smoking examined in the present study were: husband's smoking; smoking of other household members; and exposure to smoking at work. Exposure to husband's smoking was considered to start at the time of marriage or when the husband started smoking (whichever came second) and to end when the husband stopped smoking or died, or the couple separated (whichever came first). Change of husband was considered equivalent to change in husband's smoking habits, whereas single women were considered as unexposed to husband's smoking. Years of exposure to husband's smoking and average number of cigarettes smoked daily by the husband were separately examined in the analysis.

Exposure to the smoking of household members other than the husband was assessed by multiplying the years a woman lived in each of her homes throughout her life with the number of smokers in the corresponding home (excluding the husband) and by summing these product terms. Subsequently, all women were distributed into four groups: one containing those who had never been

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exposed to passive smoking from members of their household; and three corresponding to the tertiles of increasing household exposure. Finally, exposure to passive smoking in the workplace was calculated as the time-weighted sum of exposure to smoking at work, the exposure being based on the number of smokers among people working in the same closed space.

From the semi-quantitative food-frequency questionnaire, energy intake and intakes of vitamin C and of vitamin A and its constituents (carotene and retinol) were estimated by multiplying the nutrient content of the selected portion size for each specified food item, by the frequency that the food was consumed, and adding these estimates for all food items. Food-composition data were based primarily on values obtained from the University of Massachusetts Nutrient Data Base.[11] Analyses were also undertaken in order to examine food consumption (rather than nutrient intakes). Subjects were distributed into marginal quartiles by total frequency of consumption of food items belonging to specific food groups (*e.g.*, meats, fruits, and vegetables).

Multiple logistic-regression models were used for the statistical examination and summarization of the data. In the analyses, a core model was used which included age (as a categorical variable in ten-year groups), years of schooling (quantitatively), and interviewer (four indicator variables). All confidence intervals shown are 95% intervals. Analyses were done using the GLIM statistical package (Numerical Algorithms Group Inc., Release 3, 1978).

Results

Table 1 shows the distribution of cases and controls by selected demographic characteristics. There are no significant differences with respect to age, years of schooling, current residence and occupation, even though these variables were controlled for in subsequent multivariate analyses. Table 2 shows the distribution of cases and controls by selected parameters of exposure to passive smoking. There is evidence that exposure to passive smoking is associated with increased risk, but the differences are not large enough to be interpretable without controlling for confounding effects. Table 3 compares the distribution of cases and controls by lifelong exposure to outdoor air pollution. The two distributions are almost identical. Finally, in Table 4 the distribution of cases and controls by frequency of consumption of specified food groups and nutrients is presented. There is no clear or suggestive difference between cases and controls with respect to any of the indicated nutritional variables, except for cereals ($P = 0.04$) and fruits ($P = 0.11$). The association with cereals is positive but is not biologically credible, is not supported in the literature,

Table 1. Distribution of 91 non-smoking women with lung cancer and 120 non-smoking comparison women by selected demographic characteristics (percentages in parentheses)

Characteristic	Cases	Controls	P^a
Age <50 years	15 (16.5)	17 (14.2)	
50 – 59 years	18 (19.8)	22 (18.3)	0.36
60 – 69 years	27 (29.7)	31 (25.8)	
70 + years	31 (34.1)	50 (41.7)	
Schooling <1 year	18 (19.8)	27 (22.5)	
1 – 6 years	53 (58.2)	72 (60.0)	0.42
7 + years	20 (22.0)	21 (17.5)	
Current residence			
Greater Athens	48 (52.7)	67 (55.8)	
Other urban	11 (12.1)	9 (7.5)	
Semi-urban	7 (7.7)	9 (7.5)	0.99
Rural	25 (27.5)	35 (29.2)	
Occupation			
Ever employed	67 (73.6)	80 (66.7)	
Housewife	24 (26.4)	40 (33.3)	0.88
Marital status			
Ever married	83 (91.2)	109 (90.8)	
Single	8 (8.8)	11 (9.2)	0.99

[a]P value for linear trend.

Table 2. Distribution of 91 non-smoking women with lung cancer and 120 non-smoking comparison women by selected parameters of exposure to passive smoking (percentages in parentheses)

Characteristic	Cases	Controls	P^a
Husband's smoking			
Cigarettes/day			
never smoked	26 (28.9)	46 (39.7)	
1 – 20	34 (37.8)	39 (33.6)	0.16
21 – 40	22 (24.4)	22 (19.0)	
41 +	8 (8.9)	9 (7.8)	
Husband's smoking			
Duration of exposure			
never smoked	26 (28.9)	46 (39.0)	
<20 years	15 (16.7)	21 (17.8)	
20 – 29 years	15 (16.7)	20 (16.9)	0.07
30 – 39 years	17 (18.9)	15 (12.7)	
40 + years	17 (18.9)	16 (13.6)	
Other household exposure			
None	15 (16.7)	26 (22.0)	
Low (1st tertile)	29 (32.2)	26 (22.0)	0.60
Medium	24 (26.7)	27 (22.9)	
High (3rd tertile)	22 (24.4)	39 (33.0)	
Exposure at work			
Housewife	24 (27.0)	40 (33.9)	
Minimal	52 (58.4)	68 (57.6)	0.13
Some	13 (14.6)	10 (8.5)	

[a]P value for linear trend.

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Table 3. Distribution of 91 non-smoking women with lung cancer and 120 non-smoking comparison women by index of lifelong exposure to outdoor air pollution (percentages in parentheses)

Air pollution index	Cases	Controls
1st quartile: very low	32 (35.2)	43 (35.8)
2nd quartile: low	20 (22.0)	26 (21.7)
3rd quartile: moderate	18 (19.8)	22 (18.3)
4th quartile: high	21 (23.1)	29 (24.2)

P for linear trend = 0.99.

Table 4. Distribution of 91 non-smoking women with lung cancer and 120 non-smoking comparison women by approximate marginal quartiles or tertiles of frequency of consumption of specified food groups and nutrients (percentages in parentheses)

Food group or nutrient	Quartiles				P for linear trend
	1 (Low)	2	3	4 (High)	
Cereals					
cases	27 (29.7)	16 (17.6)	34 (37.4)	14 (15.4)	
controls	43 (35.8)	34 (28.3)	33 (27.5)	10 (8.3)	0.04
Potatoes					
cases	7 (7.7)	18 (19.8)	53 (58.2)	13 (14.3)	
controls	14 (11.7)	27 (22.5)	57 (47.5)	22 (18.3)	0.57
Sugars					
cases	28 (30.8)	24 (26.4)	26 (28.6)	13 (14.3)	
controls	44 (36.7)	30 (25.0)	31 (25.8)	15 (12.5)	0.40
Pulses					
cases	50 (54.9)	36 (39.6)	5 (5.5)		
controls	81 (67.5)	29 (24.2)	10 (8.3)		0.26
Vegetables					
cases	27 (29.7)	22 (24.2)	18 (19.8)	24 (26.4)	
controls	34 (28.3)	36 (30.0)	29 (24.2)	21 (17.5)	0.44
Fruits					
cases	35 (38.5)	19 (20.9)	15 (16.5)	22 (24.2)	
controls	22 (18.3)	44 (36.7)	24 (20.0)	30 (25.0)	0.11
Meats, fish, eggs					
cases	26 (28.6)	23 (25.3)	21 (23.1)	21 (23.1)	
controls	39 (32.5)	27 (22.5)	31 (25.8)	23 (19.2)	0.57
Milk and milk products					
cases	21 (23.1)	29 (31.9)	16 (17.6)	25 (27.5)	
controls	27 (22.5)	32 (26.7)	30 (25.0)	31 (25.8)	0.76
Fats and oils					
cases	25 (27.5)	24 (26.4)	33 (36.3)	9 (9.9)	
controls	35 (29.2)	30 (25.0)	33 (27.5)	22 (18.3)	0.66
Cola					
cases	70 (76.9)	10 (11.0)	11 (12.1)		
controls	95 (79.2)	16 (13.3)	9 (7.5)		0.44
Other non-alcoholic beverages					
cases	44 (48.4)	30 (33.0)	17 (18.7)		
controls	69 (57.5)	26 (21.7)	25 (20.8)		0.52
Vitamin A					
cases	23 (25.3)	21 (23.1)	20 (22.0)	27 (29.7)	
controls	30 (25.0)	32 (26.7)	32 (26.7)	26 (21.7)	0.48
Retinol (preformed)					
cases	22 (24.2)	23 (25.3)	21 (23.1)	25 (27.5)	
controls	30 (25.0)	30 (25.0)	32 (26.7)	28 (23.3)	0.72
β-carotene					
cases	25 (27.5)	19 (20.9)	20 (22.0)	27 (29.7)	
controls	28 (23.3)	33 (27.5)	33 (27.5)	26 (21.7)	0.68
Vitamin C					
cases	30 (33.0)	16 (17.6)	23 (25.3)	22 (24.2)	
controls	22 (18.3)	38 (31.7)	29 (24.2)	31 (25.8)	0.30
Total energy					
cases	23 (25.3)	25 (27.5)	18 (19.8)	25 (27.5)	
controls	30 (25.0)	27 (22.5)	35 (29.2)	28 (23.3)	0.93

is not particularly marked, and may well be explained by the multiplicity of comparisons made; it was not further explored. By contrast, the negative association with consumption of fruits is biologically credible given their high content of vitamin C and some carotenoids, and has been found in many other studies. Among the non-associations, total energy intake deserves particular attention because it indicates that, in quantitative terms, there is no differential dietary reporting between cases and controls.

The association of lung cancer with exposure to passive smoking through marriage to smoking husbands was further examined by multiple logistic regression, controlling for age, years of schooling, and interviewer. The relative risk (RR) contrasting women married to smokers with those married to non-smokers was 1.92 with CI 1.02 – 3.59. The effect of the average number of cigarettes smoked daily by the husband and the duration of marriage to smokers were evaluated in two different models, controlling for the same core variables as above and introducing, alternatively, the daily number of cigarettes and the duration of marriage as quantitative terms interacting with the smoking status of the husband (the 'gate' device).[12,13] The lung cancer risk among non-smokers increased by 16% for every 10 years of exposure to husband's smoking and by 6% for every additional pack of cigarettes smoked daily. These estimates are low and statistically non-significant – probably because, while

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the smoking status of the husband is validly ascertained, the quantitative aspects of the exposure are difficult to assess accurately.

Similar models were used to assess the effects of exposure to tobacco smoking by other household members or at the workplace. The results were qualitatively similar to those presented in Table 2. There was no evidence of any effect from exposure to smoking of other household members, whereas the effect of exposure to passive smoking at work was very small and not statistically significant (the RR between extreme quartiles was 1.08 (0.24 – 4.87)). Controlling for air pollution had no effect on any of the multivariate analyses.

Table 5 shows multiple logistic regression-derived RR for lung cancer among non-smokers between extreme quartiles of selected food groups and nutrients. The RR estimates are adjusted for age, years of schooling, interviewer, and total energy intake. There is little, if any, confounding between the two indicated food groups (vegetables and fruits) or among the three indicated nutrients. Therefore, the data suggest that fruits, but not vegetables, protect against lung cancer, and that vitamin C alone cannot explain all or most of the protective effect associated with fruit consumption. There is also evidence that retinol (preformed vitamin A), far from being protective, may actually be associated with an increased risk for lung cancer in this series.

Finally, exposure to husband's tobacco smoking, and fruit consumption, were simultaneously introduced in another model (together with age, years of schooling, interviewer, and total energy intake) to explore whether the passive smoking effect is confounded by inadequate intake of fruits, and vice versa. There is no such evidence. In fact, the RR associated with exposures to husband's tobacco smoking increased from 1.92 to 2.11 and the relative risk associated with high *vs.* low consumption of fruits decreased from 0.33 to 0.27. Introduction of cereals to the last model had no effect whereas the study was too small to allow meaningful assessment of interactive effects, if any.

The last model was also applied separately for adenocarcinomas, on one hand, and for squamous, small- and large-cell carcinomas, on the other, using in both instances the total set of controls. The results are shown in Table 6. It appears that the effects of passive smoking are more evident for squamous small- and large-cell carcinomas taken together, than for adenocarcinomas, although the difference is not statistically significant. On the contrary, the nutritional factor(s) associated with fruit consumption appear to be equally strong in both groups.

Discussion

Three major reports have concluded that the existing data strongly support a causal relation between passive smoking and lung cancer.[14 - 16] There have been also more than 10 epidemiologic studies assessing the role of nutrition in the etiology of lung cancer. In a critical review, Willett[17] summarized the evidence as being remarkably consistent in suggesting an inverse association between carotenoid sources of vitamin A and the risk of the disease. Since both exposure to passive smoking, and a diet poor in fruit and vegetables, may reflect inadequate health education, it is conceivable that each of the two factors could confound the relation of the other to the risk of lung cancer. The present study suggests that this is not the case; the effects of passive smoking and diet appear to be independent. Residual confounding on the basis of a conceivable association between husband's smoking of high tar (rather than low tar) cigarettes and inadequate fruit intake by his wife is unlikely, because high- and low-tar cigarettes confer similar exposures in the context of passive smoking (tar intake depends primarily on the filter used). Furthermore, the special effort to exclude ex-smokers from the study of lung cancer among non-smokers provides assurance that the results

Table 5. Multiple logistic regression-derived relative risk for lung cancer among non-smokers between extreme quartiles of selected food groups or nutrients

Food group or nutrient	Relative risk between extreme quartiles[a]	Confidence interval[b]	*P* value
β-Carotene	1.01	0.64 – 1.59	0.96
Retinol (preformed)	1.31	0.98 – 1.77	0.06
Vitamin C	0.67	0.42 – 1.05	0.08
Vegetables	1.09	0.44 – 2.68	0.86
Fruits	0.33	0.13 – 0.86	0.02

[a]Controlling for age, years of schooling, interviewer, and total energy intake.
[b]95 %.

Table 6. Multiple logistic regression-derived relative risk (95 % confidence intervals) for lung cancer by histologic type among non-smokers according to husband's tobacco smoking status, and to high *vs.* low quartile of fruit consumption[a]

Histological type[b]	Husband smoker *vs.* non-smoker	Fruits consumption high *vs.* low quartile
All lung cancer	2.11 (1.09 – 4.08)	0.27 (0.10 – 0.74)
Adenocarcinomas	2.04 (0.98 – 4.24)	0.22 (0.07 – 0.73)
Squamous, small- / large-cell	2.58 (0.88 – 7.57)	0.24 (0.04 – 1.36)

[a]Controlling for age, years of schooling, interviewer, and total energy intake.
[b]For 13 of the 91 cases histologic type was not available.

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of passive smoking do not reflect bias generated from misclassification of ex-smokers among the non-smokers.

The present study has advantages and disadvantages. All women were interviewed in person by medically qualified interviewers in the hospital wards; there were very few refusals, and most of the lung cancer cases were histologically or cytologically confirmed. However, the study is a hospital-based case-control investigation, and the possibility of selection bias cannot be excluded. Nevertheless, the participating hospitals admit more than one-half of the lung cancer cases and accident patients hospitalized in the Greater Athens area; cases and controls were very similar with respect to the demographic and socio-economic characteristics examined; the RR linking active smoking to lung cancer (3.3) in women is very similar to the corresponding estimates derived from other larger studies;[18] and the air-pollution findings in the present study, suggesting that there is no association between air pollution and lung cancer risk, are in line with the collective evidence in the international literature.[19,20] The appropriateness of using patients with fractures and other traumatic conditions as controls may be questioned on the basis of a postulated association between diet and osteoporosis and the well-known link between alcohol intake and risk of accident. The link between diet and osteoporosis is tenuous, however, and there is no evidence that increased intake of fruit or vegetables can lead to osteoporosis or increase the probability of a traumatic lesion through another mechanism. There is also no reason to believe that alcohol intake deserves important consideration in studies of mostly elderly Greek women, and there is no obvious link between high alcohol intake on the one hand, and low exposure to passive smoking or high intake of fruits, on the other.

The association between diet and lung cancer has been exhaustively and critically reviewed by Willett.[17] It appears that physiologic considerations and some results from animal studies have pointed to vitamin A as a possible protective factor against several tumors, in particular lung cancer. Most of the epidemiologic studies, however, provide no evidence that retinol plays an important role in the etiology of lung cancer, whereas the majority of these studies indicated that a high intake of fruits and vegetables is inversely related to the occurrence of the disease.[17] It has been assumed initially that the effect of fruits and vegetables could be explained through their high content of carotenoids, some of which are eventually converted into vitamin A. However, carotenoids may have other actions that are not shared by vitamin A – notably quenching singlet oxygen and free radicals that could otherwise initiate harmful biochemical reactions like lipid peroxidation.[21] Gradually, a consensus has begun to develop that carotenoids (and in particular, beta-carotene) are important themselves rather than as precursors of vitamin A. Although this view is certainly compatible with the empirical evidence which strongly suggests that fruits and vegetables protect against lung cancer, it is not the only credible hypothesis. As Willett[17] and other authors have warned, it is possible that other components of certain fruits and vegetables, such as carotenoids unrelated to vitamin A, or indole compounds,[22] are the protective factor(s). The findings of the present study point toward this alternative interpretation of the overall evidence. They indicate that fruits, rather than vegetables, are the important protective factors and that their effect, if real, is mediated neither through beta-carotene, nor exclusively through vitamin C.

It is possible, of course, that the results of this study, notwithstanding their statistical significance, are due to chance. It is also true that the utilized semi-quantitative food-frequency questionnaire was limited to only 47 food items and that the available nutrient database was not specifically developed to represent the Greek dietary intakes. Nevertheless, both issues cannot readily explain the pattern of associations seen in Table 5. Furthermore, these findings are compatible with the relatively low incidence of lung cancer in the Greek population – a population with the highest per capita tobacco consumption in the world, but with a very high fruit consumption as well.[23]

The findings of this study with respect to passive smoking and histologic type are compatible with findings previously reported. It is now accepted that active smoking causes all histologic forms of lung cancer but that the association is weaker for adenocarcinoma.[24] Passive smoking has been linked to adenocarcinoma[6,25] as well as to other forms of lung cancer,[3,4] but the association has been demonstrated less consistently for the former.[26,27] On the contrary, the dietary association noted in the present study does not appear to depend on histologic type, in line with the evidence emerging from other,[28] though not all,[17] previous studies.

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Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S., "Passive Smoking Among Nonsmoking Women and the Relationship Between Indoor Air Pollution and Lung Cancer Incidence-- Results of a Multicenter Case Controlled Study," Gan to Rinsho 36(3): 329-333, 1990 (translation).

This case-control study involved 120 hospitalized female cases and 519 hospitalized controls in Osaka, Japan. The authors attempted to elucidate lung cancer risk factors in nonsmoking women, with a focus on "elements in the everyday environment" rather than on occupational exposures. ETS exposure was assessed by questionnaire; only "yes/no" exposure categories are reported (e.g., there are no RRs calculated for intensity or duration exposure proxies).

Statistically nonsignificant RRs of 0.94 (95% CI 0.62-1.40) for husband's smoking and of 1.45 (95% CI 0.94-2.23) for smoking by other members of the household (usually children) were reported. For childhood exposure, a statistically nonsignificant OR of 1.71 (95% CI 0.95-3.10) was reported for maternal smoking; for paternal smoking, a statistically significantly reduced risk (RR = 0.60, 95% CI 0.40-0.91) was reported for a univariate analysis.

The relationships of various types of room heaters to lung cancer were considered. No significant relationships were reported for unvented stoves using gasoline, gas, coal, charcoal briquettes or wood; or for braziers, clay charcoal stoves, or foot warmers using charcoal. The data suggested that past use of straw or wood as a cooking fuel may be a risk factor for lung cancer among nonsmoking women (for use at age 30, RR = 1.90, 95% CI 1.09-3.30; at age 15, RR = 1.33, 95% CI 0.87-2.02).

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Sobue*1, T., R. Suzuki*1, N. Nakayama*1, C. Inubuse*1, M. Matsuda*2, O. Doi*3, T. Mori*4, K. Furuse*5, M. Fukuoka*6, T. Yasumitsu*7, O. Kuwabara*8, M. Ichigaya*9, M. Kurata*10, M. Kuwabara*11, K. Nakahara*12, S. Endo*13, and S. Hattori*13: PASSIVE SMOKING AMONG NONSMOKING WOMEN AND THE RELATIONSHIP BETWEEN INDOOR AIR POLLUTION AND LUNG CANCER INCIDENCE--RESULTS OF A MULTICENTER CASE CONTROLLED STUDY. Gan to Rinsho, Vol. 36, No. 3, pp.329-333. 1990.

Introduction

According to the 1987 population dynamics statistics compiled by the Ministry of Health and Welfare, the age-adjusted mortality of lung cancer in both men and women is the second highest (after stomach cancer) among cancer mortalities[1]. The age-adjusted mortality in stomach cancer has been steadily declining since 1960, while that of lung cancer has been rapidly increasing during the same period. If this trend continues, the ranking of these mortalities will be reversed by the year 2000[2].

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*1 Survey Section, Osaka Prefectural Adult Disease Center.
*2 Department of Internal Medicine, Osaka Prefectural Adult Disease Center.
*3 Department of Surgery, Osaka Prefectural Adult Disease Center.
*4 Department of Surgery, National Sanatorium Kinki Central Hospital.
*5 Department of Internal Medicine, National Sanatorium Kinki Central Hospital.
*6 Department of Internal Medicine, Osaka Prefectural Habikino Hospital.
*7 Department of Surgery, Osaka Prefectural Habikino Hospital.
*8 Department of Internal Medicine, National Sanatorium Toneyama Hospital.
*9 Department of Respiratory Diseases, Osaka Red Cross Hospital
*10 Department of Thoracic Surgery, Kitano Hospital.
*11 Department of Respiratory Diseases, Kansai Denryoku Hospital.
*12 The First Department of Surgery, Osaka University School of Medicine.
*13 The Organization to Eliminate Lung Cancer from Osaka.

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For risk factors to explain this rising incidence of lung cancer, smoking is cited first. In Japan, the incidence of smoking among men has been declining in recent years but it was reported to be 55% in 1988[3], a rate considerably higher in comparison to the incidences in the western world. Thus the promotion of an antismoking policy is considered to be necessary. Although the incidence of smoking has recently been increasing among young women, it was reported to be mere a 9%[3] in 1988, a figure much lower than those in western societies. To reflect this situation, the population-attributable risk of lung cancer due to smoking is 71% in men and only 26% in women[4]. In other words, it is suggested that risk factors other than smoking exist in the development of lung cancer among women.

In the past, for risk factors other than smoking that cause lung cancer to develop, studies have been conducted with a major focus on occupational exposure. In women, however, it is necessary that studies on exposure to various elements in the everyday environment supersede the investigation of the effects of occupational factors. However the relative risk of these elements in everyday environment is expected to be comparatively small. Thus it is necessary to include as many cases of lung cancer among nonsmoking women as possible for the analysis.

The purpose of the present study is to elucidate the risk factors of lung cancer among nonsmoking women. Therefore the status of passive smoking and the relationship between indoor air pollution and the development of lung cancer were investigated, using the data from the case-controlled studies conducted jointly by a number of health facilities. It should be noted that the study uses data collected up to the end of March 1989; thus the figures may be different in the final section of the report which is scheduled for the coming year.

1. Subjects and Method.

The "Organization to Eliminate Lung Cancer from Osaka"[3], with the participation of 8 major hospitals in Osaka specializing in the treatment of lung cancer, has been conducting a hospital-based case-controlled study since January 1986. Among the

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patients newly admitted with a diagnosis of primary lung cancer, 658 men and 193 women were registered by the end of March 1989. Only 23 out of these 658 men (3.5%) were lifetime nonsmokers. Among the 193 female patients, however, 120 (62%) were nonsmokers. The present analysis was limited to these nonsmoking female patients. Of the lung cancers in these nonsmoking women, 78% were classified as adenocarcinoma.

For control, 519 nonsmoking female patients were selected from those newly admitted to the same hospitals with a diagnosis other than lung cancer. Neoplastic diseases were the predominant diagnosis (85%) of these patients. Breast cancer (240 cases) was the most common, followed by stomach cancer (63 cases). For the analysis, the ages criteria at the time of admission was set from 40 to 79 years for both the lung cancer patients and control.

The information on smoking and indoor air pollution was obtained from a questionnaire, filled out by the patients, which was distributed and collected at the time of admission. Any questionable responses concerning the present analysis were excluded from tabulation. Medical information such as histological type of cancer was obtained from attending physicians. The age-adjusted odds ratio and 95% confidence level were computed by the Mantel-Haenszel method using the PROC FREQ of SAS[6]. Factors with an estimated value of the odds ratio over 1.5 or below 0.67 were selected and subjected to a logistic regression analysis using PROC LOGIST of SAS[7].

2. Results

Table 1 shows an age-adjusted odds ratio where the population was divided into those with smoking husbands and other members of the family who were smokers. The table was prepared to find the effects of passive smoking on lung cancer in adults (prior to hospital admission). The odds ratio when the husbands were smokers was almost 1 (0.94), while smoking by other members in the household raised it to 1.43, indicating a slight increase in risk. Most of the other smoking members in a household were children.

To find the effects of passive smoking during early

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childhood, the age-adjusted odds ratios were computed when fathers, mothers, or other members of the household were smokers. The results are shown in Table 2. When fathers were smokers, the odds ratio of passive smoking was 0.60, with a significant reduction in risk. When mothers were smokers, the odds ratio was computed to be 1.71. The risk rose in this instance but the change was not significant. The odds ratio for smoking by other members of the families was computed to be 1.13.

Table 3 shows the effects of using room heaters (which may be a cause of indoor air pollution) on the development of lung cancer as an age-adjusted odds ratio. The ratio was computed separately for each age category when the heater was in use. For heating facilities which may be the cause of indoor air pollution the following were included: unvented stoves using gasoline, gas, coal, charcoal briquettes, or wood; or a brazier, clay charcoal stove, or foot warmer which burns charcoal or briquettes. Air conditioners, stoves with vents, electric stoves, and electric foot warmers were excluded from the study. Odds ratios were computed in relation to the use of these sources of pollution at each age level when the heaters were used. As shown in Table 3, the ratios were near 1 for each age level, showing no significant relationship.

The effects of using foot warmers (burning charcoal, small briquettes, or round briquettes for the source of heat when sleeping) on the incidence of lung cancer were studied and expressed as an age-adjusted odds ratio in Table 4. These ratios, shown by age level, were near 1 for all ages, indicating no significant relationship.

Next, age-adjusted odds ratios were computed for the effects of using straw or wood for cooking on the development of lung cancer (Table 5). Again, the ratios were computed for each group. The ratio was 1.33 when the fuel was used at age 15 and 1.90 when used at age 30, with the latter showing a statistical significance. All the patients who had been using straw or wood for cooking at age 30 had also used the same fuel at age 15. Therefore the odds ratio computed at age 30 was interpreted to

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express the effect of long-term exposure to this source of pollution. None of the patients was still using straw or wood as a source of cooking heat.

In these analyses, the odds ratios for the following 3 situations were computed to be over 1.5 or less than 0.67: smoking by father or mother when the patient was young and the use of straw or wood as the source of cooking heat at age 30. Using these 3 situations as variables, the odds ratio was estimated using a logistic regression model (Table 6). It was found that only the use of straw or wood as the source of cooking heat at age 30 showed a statistical significance.

3. Discussion

The results of the present study suggested that the use of straw or wood as a cooking fuel in the past is a risk factor in the development of lung cancer among nonsmoking women. Gao, et al.[9] investigated women in Shanghai and reported that the use of rapeseed oil raises the risk of lung cancer by 40%. In the same report, the use of cooking fuel (coal, city gas, and wood) did not increase the risk. Koo, et al.[8] conducted a study on women residing in Hong Kong and reported that among cooking fuels, the use of petroleum increases the risk of lung cancer while the risk is lower when propane gas (LPG) is used. However they added that these effects are relatively insignificant. MacLennan, et al.[10] conducted a study on Chinese women in Singapore and reported that there was no difference with respect to the risk of lung cancer when wood or charcoal used as cooking fuel was compared against petroleum and gas. The subjects of these studies were all Chinese women. In addition, exposure was based on whether the subjects ever used the fuel in question at all in the past or whether they are currently using it. Such criteria may not necessarily reflect past exposure accurately. Furthermore there is a possibility that those who were classified as "not exposed" may actually have been substantially exposed. If these possibilities are taken into consideration, the results of these studies do not necessarily contradict ours.

No subjects currently use straw or wood for cooking fuel so

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we could not institute a policy of primary prevention of lung cancer in relation to this practice. However the finding is considered significant in suggesting that some factor(s) closely related to our daily lives may be recognized as risk factor(s) for lung cancer that appears 10 or 20 years later.

No statistical significance was obtained from the effect of maternal smoking when the subjects were young. However the estimated odds ratio was high (1.79) and the power to detect the significant difference from the cases of the present study was computed to be 56%. Therefore further studies with a larger number of subjects are considered necessary. As for the short-term effect of maternal smoking on the health of children, Tager, et al.[11] reported that the respiratory function was depressed in children when parents were smokers and the tendency was exaggerated when the mothers were smokers. Wu, et al.[12] conducted a case-controlled study on white women in Los Angeles but they failed to find a significant relationship between lung cancer and maternal smoking. In Japan, Shimizu, et al.[13] reported an odds ratio of 1.6 for maternal smoking in relation to lung cancer in women.

In the present study, the risk of lung cancer from paternal smoking was significantly reduced in a single variate analysis but the results of a multivariate analysis were not significant. Compared with the mother, the time a child spends with her father is expected to be short; and the tendency towards a decline in risk is believed to be due to some confounding factor (such as social class).

For the effect of passive smoking during adulthood, the present study focused on smoking by husbands but no significant correlation with lung cancer was established. In Japan, Hirayama[14], and Akiba, et al[15] found a significnat relationship between the two but Shimizu, et al.[13] did not. Blot, et al.[16] conducted a meta analysis based on epidemiological data throughout the world and estimated that husbands' smoking raises wives' risk for lung cancer by 30%. The 95% confidence range of the odds ratio in the present study is 0.62 to 1.40 and includes

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1.30 within but a clearcut conclusion could not be drawn from such an uncertain risk factor. The present study also indicated that the effect of smoking by other members of the household, rather than by husbands, tends to be more significant. Shimizu, et al.[13] reported that smoking by fathers-in-law who lived in the same households has a more significant effect than that by husbands.

The analysis in the present study failed to show an increase in the risk of lung cancer in relation to the use of heating equipment. For the use of various heating devices, Leung[17] reported that the use of petroleum stoves raised the risk of lung cancer among women in Hong Kong. In Japan, however, Shimizu[18] conducted a case-controlled study in Nagoya in which no increase in the risk of lung cancer was recognized in association with the use of petroleum stoves.

The most serious problem inherent in the methodology of the present study is a large number of cancer patients (especially those with breast cancer) included in the control. Both the cases and control were nonsmokers and there have been no reports on the relationship between the exposure factor--the subject of the present analysis--and cancer involving other organs. Therefore inclusion of a large number of cancer patients is not considered to present a serious problem. However dominance by a single clinical entity (breast cancer in this instance) is not desirable in view of the nature of the control.

The authors plan further studies using a larger number of patients and an improved analysis of the control.

The authors express their gratitude to Dr. Hanai (Osaka Adult Disease Center) who prepared the original form of the questionnaire for the present survey under the guidance of Dr. Muir (IARC).

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Table 1. Odds Ratio of Passive Smoking in Adulthood (before Hospitalization)

	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
Smoking by Husband		
no	56/229	1.00
yes	64/200	0.94(0.62-1.40)
Smoking by Other Members		
no	77/384	1.00
yes	43/135	1/45(0.94-2.23)

* Adjusted by age at hospital admission.

Table 2. Odds Ratio of Passive Smoking during Childhood

	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
Smoking by Father		
no	47/144	1.00
yes	73/375	0.60(0.40-0.91)
Smoking by Mother		
no	102/473	1.00
yes	18/46	1.71(0.95-3.10)
Smoking by Other Members		
no	95/416	1.00
yes	25/103	1.13(0.69-1.87)

* Adjusted by age at hospital admission.

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Table 3. Odds Ratio When Heating Equipment Which May Be The Cause of Indoor Air Pollution Is Used--Observation in Relation to the Age When the Equipment Was Used

Use of Equipment	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
At Age 15		
not used	37/150	1.00
used	83/369	0.94(0.60-1.45)
At Age 30		
not used	45/212	1.00
used	75/307	1.09(0.72-1.65)
At Present		
not used	65/289	1.00
used	55/230	1.07(0.71-1.60)

* Adjusted by age at admission.

Table 4. Odds Ratio When Foot Warmers Were Used During Sleep--Observation at Each Age Level

Use of the Equipment	Lung Cancer/control	Odds Ratio* (95% Confidence Level)
At Age 15		
not used	76/327	1.00
used	44/192	0.97(0.64-1.47)
At Age 30		
not used	95/429	1.00
used	25/90	0.89(0.53-1.51)
At Present		
not used	119/514	1.00
used	1/5	0.67(0.09-4.99)

* Adjusted by age at hospital admission.

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Table 5. Odds Ratio When Straw and Wood Are Used for Cooking Fuel

Use of the Fuel	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
At Age 15		
not used	46/252	1.00
used	74/267	1.33(0.87-2.02)
At Age 30		
not used	94/469	1.00
used	26/ 50	1.90(1.09-3.30)
At Present		
not used	123/519	-
used	0/0	-

* Adjusted by age at hospital admission.

Table 6. Age-Adjusted Odds Ratios for Maternal and Paternal Smoking during Childhood; and the Use of Straw and Wood as a Cooking Fuel at Age 30, Calculated by Logistic Regression Analysis

Factors	Odds Ratios (95% Confidence Level)
Maternal Smoking During Childhood	1.82(0.98 - 3.37)
Paternal Smoking During Childhood	0.70(0.43 - 1.16)
Use of Straw and Wood as Cooking Fuel at Age 30	1.78(1.02 - 3.10)

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Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.

This case-control study (965 cases, 959 controls) includes female lung cancer cases from Shenyang and Harbin, northeast China, two industrial cities with particularly high rates of lung cancer. The sample was composed of 518 cases and 555 controls from Shenyang and 446 cases and 404 controls from Harbin. [The Shenyang females may be the same sample used by Xu, et al., 1990.] Age-matched neighborhood controls were chosen using a randomized procedure. Cytological confirmation was available for 74% of the cases. The questionnaire utilized covered such areas as demography, active and "passive" smoking, lifetime residential and occupational histories, diet, heating and cooking practices, personal history of lung disease, family history of tuberculosis and lung cancer, and reproductive factors. The authors reported that cigarette smoking was a major risk factor for lung cancer.

The RR calculated for spousal smoking was statistically significantly negative (RR = 0.7, 95% CI 0.6-0.9, $p < 0.05$); the sample size was 343 cases and 515 controls. Workplace ETS exposure was reported to have a RR of 1.1 (95% CI 0.9-1.6) for nonsmokers.

RRs for lung cancer in the range of 1.1-1.6 were reported for exposure to air pollution from coal-burning stoves, "kang," or other indigenous heating devices. Elevated risks were also associated with deep frying (e.g., two or more times per month, RR = 2.1, 95% CI 1.5-2.8) and with eye irritation during cooking. Statistically significant increased risks were reported for employment as a smelter worker (RR = 1.5, 95% CI 1.0-2.1) and for occupational exposures to coal dust and to smoke from burning fuel. Personal history of lung disease (RR 1.5, 95% CI 1.2-1.8) and family history of tuberculosis (RR = 1.6, 95% CI 1.2-2.1) and lung cancer (RR = 1.8, 95% CI 1.1-3.0) were associated with increased risk as well. There was no protective effect of intake of carotene-rich vegetables; however, overall carotene intake was high in this population.

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Lung cancer among women in north-east China

A.H. Wu-Williams[1], X.D. Dai[3], W. Blot[2], Z.Y. Xu[4], X.W. Sun[3], H.P. Xiao[4], B.J. Stone[2], S.F. Yu[3], Y.P. Feng[4], A.G. Ershow[2], J. Sun[4], J.F. Fraumeni Jr[2] & B.E. Henderson[1]

[1]Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, CA 90033, USA; [2]National Cancer Institute, Bethesda, MD 20892, USA; [3]Harbin Medical School, Harbin, Heilongjiang Province, People's Republic of China; and [4]Liaoning Public Health and Anti-Epidemic Station, Shenyang, Liaoning Province, People's Republic of China.

Summary A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities which have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumours among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to 'Kang' and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung.

The rate of lung cancer among Chinese females is among the highest in the world. Elevated incidence, particularly of adenocarcinoma of the lung, has been noted for Chinese females residing in different geographic areas, including Singapore (Law *et al.*, 1976), Hong Kong (Kung *et al.*, 1984), Shanghai (Gao *et al.*, 1988) and the United States (Hinds *et al.*, 1981). The high rates are unusual because few Chinese women smoke tobacco. Within China, elevated rates of female lung cancer are found in urban areas such as Shanghai and in rural as well as urban areas of the northeastern provinces of Liaoning and Heilongjiang (National Cancer Control Office, 1980; Xu *et al.*, 1986). Reasons for the geographic variation and clustering of high rates of lung cancer in the northern provinces are not known. We report here the results from case-control studies conducted in Shenyang and Harbin, the two major industrial cities in Liaoning and Heilonjiang provinces, to evaluate the role of several potential risk factors.

Methods

In 1985-87, investigators from the Liaoning Province Public Health and Anti-Epidemic Station and the US National Cancer Institute conducted a large lung cancer study including 1,517 males (729 cases, 788 controls) and 1,073 females (518 cases, 555 controls). During the same time period, investigators at Harbin Medical College and the University of Southern California conducted a case-control study focused on female lung cancer (446 cases, 404 controls). Investigators from both studies met during the planning phase of the study and adopted a unified protocol to ascertain and select cases and controls, and a common questionnaire for the interview component of the study. Data on risks from smoking and air pollution among men and women in Shenyang have been published elsewhere (Xu *et al.*, 1989). Herein we report risks among females associated with a variety of factors, increasing sample sizes by nearly 80% by combining information from the two cities.

Correspondence: A.H. Wu-Williams.

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Case ascertainment

We sought to enrol all newly diagnosed primary lung cancers in females in the study areas between 1985 and 1987. Utilising the cancer registries of Harbin and Shenyang, a system of rapid case ascertainment was established with the cooperation of all the major hospitals serving its area (about 35 in each city). In brief, the admitting physicians at each participating hospital completed a case abstract form whenever a lung cancer was diagnosed. We received these abstracts on a bi-weekly basis and selected as eligible cases those with primary, incident lung cancers diagnosed among female residents of the study area who were aged less than 70 years at the time of diagnosis. The lung cancer diagnosis and cell-type classification were verified locally in each study area by a panel of pulmonary specialists and pathologists.

Control selection

Controls were females randomly selected from the general populations of Harbin and Shenyang. Controls were frequently matched by 5-year age group to the expected distribution of cases, which was determined in advance using the number and age distribution of female lung cancer cases reported in the two cities in 1983. A three-stage sampling procedure was used to select each control. The initial unit for randomization was the neighbourhood committee, of which there are about 1,500 each in Harbin and in Shenyang. Committees were randomly selected with replacement after weighting by their population sizes. Then we randomly chose a household group from the approximately 10-25 household groups within each selected neighbourhood committee. In the final stage, among all females in the 5-year age category within the household group, one was randomly selected.

Questionnaire

A structured, pre-coded questionnaire was used by trained interviewers who conducted personal interviews with the participants in their homes or work sites or in the hospital/clinic. The interview gathered information on demographic factors, active and passive smoke exposure, lifetime residential and occupational histories, diet and cooking practices, personal history of noncancer lung diseases, history of tuberculosis

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(TB) and cancer in first degree relatives, and reproductive factors. Questions on smoking included the amount and types of tobacco products smoked, age when smoking started, and for ex-smokers, age when smoking stopped. To assess passive smoke exposure, we asked about lifetime residential exposure to tobacco smoke from cohabitants, including the amount and duration of exposure from each smoking cohabitant. In addition, we asked if the subject was exposed to passive smoking at each work place. For each residence in which a subject lived for three or more years, we asked in detail about heating and cooking practices, including methods for heating and cooking and types of fuels used. Several questions were asked about 'Kang', brick beds commonly used in the north-eastern part of China, which are heated either directly by a stove underneath them or by pipes connected to the cooking stove. To assess dietary habits 5 years prior to interview, we asked subjects to estimate their frequencies of intake of 33 food items, including staple grains (rice, wheat, maize), soya bean products (bean curd, fermented bean paste), dried peas and beans, animal protein sources (eggs, fish, shellfish, liver, poultry, pork), fermented/salted foods, alcoholic beverages, and fresh vegetables and fruits. Also included were questions on diagnosis by a physician of previous each lung diseases, age at lung disease diagnosis, and if hospitalisation was required. Information on outcome of each pregnancy, age at menarche and at menopause was also elicited. As a quality-control measure, interviews were cassette-recorded for review by a field supervisor.

Statistical methods

The data were edited, coded, keypunched and submitted to computerised range and consistency checks. The statistical analyses were based on multivariate techniques for case-control data (Breslow & Day, 1980). Unconditional logistic regression analyses were used to estimate summary relative risks (RRs) of lung cancer associated with various factors while adjusting for other factors. RRs were calculated for all lung cancer combined and for specific cell types. We present results for squamous cell and oat/small cell cancers combined because we had too few oat/small cell cancers to conduct separate analysis and because these two cell types of lung cancer are more strongly associated with smoking than adenocarcinoma of the lung (Lubin & Blot, 1984). Our analysis for adenocarcinoma of the lung did not include large cell cancers. There were too few large cell cancers for inclusion by cell type. In the analyses including all subjects, the regression models contained terms for age (less than 50, 50–59, 60–69 years), education (no formal education, primary or secondary school, high school and higher), smoking (non-smoker, smoked 1–19 cigarettes per day and 1–29 years, 1–19 cigarettes per day and 30–39 years, 1–19 cigarettes per day and 40+ years, 20+ cigarettes per day and 1–29 years, 20+ cigarettes per day and 30–39 years, 20+ cigarettes per day and 40+ years) and study centre (Harbin versus Shenyang). We also conducted analyses restricted to nonsmokers, deleting the smoking variables in the regression model and adjusting only on age, education, and centre.

Results

All interviews were conducted in 1985–87. At the close of case recruitment, 1,049 eligible patients had been identified by the Harbin and Shenyang cancer registries. Nine-hundred and sixty-four (91.8%) were interviewed, 32 (3.1%) died before our attempted contact, 50 (4.8%) were not located and three (0.3%) refused to participate.

Forty-two per cent ($n = 405$) of the cases were diagnosed by tissue biopsy, 32% ($n = 309$) by cytology, and 26% ($n = 351$) by radiology. Although the percentages of pathologically and cytologically confirmed cases were higher in Shenyang than in Harbin, the cell-type distributions were similar. In the combined set of cases, there were 44% ($n = 310$) adenocarcinomas, 28% ($n = 201$) squamous cell carcinomas, 16% ($n = 117$) oat/small cell carcinomas and the remainder were large cell carcinomas, mixtures of other cell types or the cell type was not known ($n = 66$).

A total of 959 controls (404 in Harbin, 555 in Shenyang) were interviewed. Cases (mean age 55.9 years) and controls (mean age 55.4 years) were closely matched on age but cases were less educated than controls. Relative to those with no formal education, the RRs for women with primary/junior school, high school/technical school or college education was 0.9, 1.0, 0.8 respectively (RR for linear trend 0.9; 95% CI 0.8–1.0).

Smoking habits

Table I shows the percentages of women by 5-year age group who smoked cigarettes for 6 months or longer. The prevalence of smoking in the general population (i.e. among controls) varied with age, being much higher (approximately 40%) among women 50 or over than among women below 50 (smoking rate 24%), but increased risks were seen in smokers at all ages. For all lung cancers combined, smokers experienced a 2.3-fold (95% CI 1.9–2.8) increased risk of lung cancer. The age-, education- and city-adjusted RRs for smoking were 4.2 (95% CI 3.0–5.9) for squamous cell cancer, 2.2 (95% CI 1.4–3.2) for oat/small cell cancers, 1.5 (95% CI 1.1–1.9) for adenocarcinoma of the lung and 2.5 (95% CI 1.9–3.3) for the 'other' category which included those diagnosed clinically, large cell cancers, and those with mixed or unknown cell type. Most (57%) cases began smoking before they were 20 years old, compared to 40% of controls; the average age when subjects began to smoke was 19.9 for cases and 24.0 for controls. The women were not heavy smokers. Few subjects (9% cases, 4% controls) smoked 20 or more cigarettes per day, and the mean daily number of cigarettes smoked was 8.1 for cases and 6.8 for controls. Nevertheless, there was sufficient variation in amounts smoked to show that risks of lung cancer significantly ($P < 0.001$) increased with increasing numbers of cigarettes smoked per day and with increasing duration of smoking (Table II). Clear independent effects were seen with each measure of smoking exposure within categories of the other, with the associations stronger for squamous/oat cell carcinomas than for adenocarcinoma. At the same level of smoking, 2- to 4-fold differences in the magnitude of the risk between the two cell types were typically observed.

Passive smoking

Table III shows the RRs associated with passive smoke exposure, first among all subjects after adjusting for personal smoking and then among non-smokers. Eighty-eight per cent of all cases and controls reported having lived in at least one of their residences with a cohabitant who was a smoker. There were no significant case–control differences in ever having lived with a smoker, except for non-smokers who lived with a spouse who smoked, where the risk was reduced (RR 0.7; 95% CI 0.6–0.9). The lowered risk associated with a spouse who smoked was seen only in Harbin: 60% of non-smoking controls and 46% of non-smoking cases in Harbin reported that the spouse ever smoked, compared to 52% of non-smoking controls and 52% of non-smoking

Table I Prevalence of smoking by 5-year age groups and corresponding relative risks for lung cancer associated with smoking

	Cases		Controls			
Age (years)	*n*	*% smokers*	*n*	*% smokers*	*RR*	*(95% CI)*
<50	208	34	163	24	1.6	(1.0, 2.6)
50–54	203	60	196	35	2.7	(1.8, 4.0)
55–59	232	62	241	43	2.0	(1.4, 3.0)
60–64	184	68	191	39	3.2	(2.1, 5.0)
65+	137	60	161	40	2.2	(1.4, 3.5)

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Table II RR and 95% CI for lung cancer associated with intensity of smoking by cell type

Cell type	Cigarettes per day	Duration of smoking (years) 1-29		30-39		>40	
All lung cancer	1-19	1.3 (1.0, 1.7)[a]	(118/125)[b]	2.6 (1.9, 3.5)	(146/83)	3.2 (2.4, 4.3)	(187/103)
	≥20	1.8 (0.9, 3.6)	(19/14)	3.3 (1.8, 6.2)	(33/15)	5.7 (2.9, 11.5)	(36/11)
Squamous oat cell	1-19	2.0 (1.3, 2.9)	(48/125)	3.9 (2.6, 5.9)	(56/83)	4.7 (3.1, 7.1)	(64/103)
	≥20	2.0 (0.7, 5.4)	(6/14)	3.8 (1.7, 8.8)	(10/15)	12.0 (5.3, 27.0)	(17/11)
Adenocarcinoma	1-19	0.8 (0.5, 1.3)	(30/125)	1.7 (1.1, 2.5)	(37/83)	2.0 (1.3, 3.0)	(45/103)
	≥20	0.8 (0.3, 2.6)	(4/14)	3.8 (1.8, 8.0)	(15/15)	2.8 (1.0, 7.4)	(7/11)

[a]95% confidence intervals. [b]Numbers of cases/controls are in parentheses.

Table III RR for lung cancer associated with passive smoke exposure

Source of passive smoke exposure	Passive smoke exposure	All subjects Case/controls	RR[a]	Non-smokers only Case/controls	RR[a]
Any cohabitant	no	112/111		74/87	
	yes	844/842	0.8	343/515	0.7
Spouse	no	398/402		212/271	
	yes	558/551	0.9	205/331	0.7[b]
Mother	no	543/595		298/410	
	yes	413/358	1.0	119/192	0.9
Father	no	484/515		235/352	
	yes	472/438	1.0	182/250	1.1
Workplace	no	403/448		187/301	
	yes	563/513	1.2	228/301	1.1

[a]Adjusted for age, education, personal smoking and study area. [b]Adjusted for age, education, and study area. [c]$P < 0.05$.

cases in Shenyang. There were no significant trends in risk with intensity (i.e. number of cigarettes smoked by family members) and duration of exposure (i.e. years of smoking by cohabitants), except for an increasing risk associated with increasing intensity of father's smoking in the presence of the index subject.

There was a small excess risk associated with passive smoke exposure at the workplace. For all subjects, the smoking-adjusted RR was 1.2 (95% CI 1.0–1.4). The result was similar for non-smokers (RR 1.1; 95% CI 0.9–1.6). There were no significant dose–response trends associated with years of passive smoke exposure at work.

Heating and cooking practices

Table IV presents RRs associated with duration of use of Kang and other heating devices. Elevated risks were observed for increasing years of use of Kang (particularly when heated by stoves underneath), heated brick walls or floors (i.e. heated by pipes leading from the stoves to the wall or floor), coal stoves and coal burners. On the other hand, decreased risks were observed for increasing years of use of non-coal-burning stoves and central heating. The patterns were generally similar for smokers and non-smokers, and for squamous/oat cell carcinomas and adenocarcinoma. We also examined the risks associated with years when coal, wood, and central heating served as the main fuel for heating. The RRs tended to rise with increasing use of coal and decline with increasing use of wood and central heating, but none of the trends was significant.

Cases more often reported that their homes became smoky during cooking and that they more frequently had irritated eyes during cooking (Table V). There also was a significant trend in risk with increasing number of meals cooked by deep frying, although this method of cooking was not frequently used. The results were similar for squamous/oat cell cancers and adenocarcinoma, and for smokers and non-smokers.

Occupation

Subjects were asked about all jobs in which they had worked 1 or more years, with cases and controls compared in terms of their employment in 29 job categories. Most (77%) women held at least one job outside the home, but significantly increased risks were observed only for metal smelting work (RR 1.5; 95% CI 1.0–2.1), while a significantly decreased risk was observed for textile workers (RR 0.6; 95% CI 0.3–1.0). The women were also asked if they were exposed to 12 specific dusts, smoke or fumes at work, with from 1 to 16% reporting on-the-job exposures to the 12 pollution items. Cases reported exposure to coal dust (RR 1.5; 95% CI 1.1–2.0) and to smoke from burning fuel (RR 1.6; 95% CI 1.2–2.2) significantly more often.

Table IV Relative risk of lung cancer associated with years of use of specific heating devices

Exposure (years)	Case/controls	RR[a] (95% CI)
Kang		
0	25/40	1.0
1-39	384/376	1.4 (0.8, 2.4)
40-49	132/144	1.1 (0.6, 2.8)
50+	415/393	1.6 (0.9, 2.8)
Burning Kangs		
0	677/740	1.0
1-20	106/91	1.2 (0.9, 1.7)
21+	173/122	1.5 (1.1, 2.0)
Coal stoves		
0-20	192/226	1.0
21-40	511/485	1.2 (1.0, 1.6)
41+	253/242	1.3 (1.0, 1.7)
Non-coal stoves		
0	212/183	1.0
1-20	367/340	0.8 (0.6, 1.1)
21-30	259/295	0.7 (0.5, 0.9)
31+	118/135	0.8 (0.5, 1.1)
Heated brick walls/floors		
0	586/651	1.0
1-20	127/98	1.5 (1.1, 2.1)
21+	243/204	1.4 (1.1, 1.9)
Coal burners		
0	525/583	1.0
1-20	258/202	1.2 (1.0, 1.6)
21+	173/168	1.1 (0.8, 1.4)
Central heat		
0	602/573	1.0
1-20	215/200	1.0 (0.8, 1.3)
21+	139/180	0.8 (0.6, 1.0)

[a]Adjusted for age, education, personal smoking and study area.

Table V Relative risk of lung cancer associated with frequency of deep frying and eye irritation when cooking

	Cases/controls	RR[a] (95% CI)
Deep fry (times per month)		
0	324/403	1.0
1	326/360	1.2 (1.0, 1.5)
2	170/107	2.1 (1.5, 2.8)
3+	121/81	1.9 (1.4, 2.7)
Eye irritation		
never/rarely	647/732	1.0
sometimes	218/163	1.6 (1.2, 1.8)
frequent	89/56	1.8 (1.3, 2.6)

[a]Adjusted for age, education, personal smoking and study area.

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Prior lung disease

Table VI lists RRs of lung cancer associated with specific prior chronic lung diseases. Lung diseases that were first diagnosed within three years of lung cancer diagnosis (and a comparable time period for controls) were excluded from the analysis. After adjusting for smoking, history of any prior lung disease was associated with a 50% increased risk (95% CI 1.2–1.8). The excess was greatest for pneumonia (RR 2.1). An increased risk was found for bronchitis and/or emphysema, but the association was limited to squamous/oat cell cancers (RR 1.6) and not found for adenocarcinoma (RR 0.9).

We investigated whether risk of lung cancer varied according to the lag time following the diagnosis of prior lung disease. Earlier detection of chronic bronchitis/emphysema conveyed greater risk. Relative to those with no history of chronic bronchitis/emphysema, the RRs were 1.3, 1.3, and 1.7 respectively for conditions detected 4–10, 11–20, and 21+ years before lung cancer diagnosis. On the other hand, the RRs were higher for more recent diagnoses of pneumonia and TB. The RRs were 2.7, 2.5 and 1.8 respectively for pneumonia, and 2.8, 1.1, and 1.2 for TB first detected 4–10, 11–20 and 21+ years prior to lung cancer diagnosis. The elevated risk associated with TB diagnosed 4–10 years prior to lung cancer was significant; it was observed for both squamous/oat cell cancers and adenocarcinoma of the lung, and among non-smokers as well as smokers.

Family history of TB and cancer

We observed a significant 60% (95% CI 1.2–2.1) increased risk associated with TB in a household member, with similar risks for squamous/oat cell cancers and adenocarcinoma. The familial association was seen in smokers and non-smokers, and remained unchanged after adjusting for personal history of TB. The risk associated with family history of TB increased with decreasing age when the index subject was first exposed. After adjusting for smoking, exposures at age <21, 21–30 and >30 conferred risks of 1.7, 1.5 and 1.2 when compared to those with no household TB exposure.

Family history of lung cancer in first degree relatives, reported by 4.5% of the cases, was associated with a significant 80% (95% CI 1.1–3.0) increased risk. There was little difference in risk by cell type or smoking status. The risk of lung cancer was somewhat higher among those with a family history of other cancers (RR 1.4; 95% CI 1.0–2.0), with the excess risk being higher for adenocarcinoma (RR 1.8) than for squamous/oat cell cancers (RR 1.1).

Menstrual and reproductive factors

Table VII presents risks of lung cancer by various menstrual and reproductive factors. There were little or no association with age at menarche, parity, hysterectomy, spontaneous abortion, pregnancy resulting in difficult labour, and use of oral contraceptives. There was a significant 50% (95% CI 1.2–1.8) increased risk associated with history of miscarriage, and cases tended to have a later age at natural menopause although the trend was not smooth.

Table VII Relative risks of lung cancer associated with menstrual and reproductive factors

	Cases/controls	RR* (95% CI)
Age at menarche		
18+	184/192	1.0
16–17	427/412	1.1 (0.8, 1.4)
14–15	285/276	1.1 (0.8, 1.4)
<14	55/64	0.9 (0.6, 1.4)
Number of children		
<3	193/205	1.0
3–4	319/300	1.1 (0.9, 1.5)
5–6	275/272	1.0 (0.8, 1.4)
7+	169/174	1.0 (0.7, 1.3)
Age at natural menopause		
<45	77/112	1.0
45–49	373/303	1.7 (1.2, 2.4)
50–54	278/327	1.3 (0.9, 1.8)
55+	31/28	1.7 (1.0, 3.2)
Positive history of		
Hysterectomy	36/36	1.0 (0.6, 1.6)
Miscarriage	82/126	1.5 (1.2, 1.8)
Spont. abortion	239/218	1.1 (0.9, 1.4)
Difficult labour	76/61	1.3 (0.9, 1.8)
Oral contraceptive	54/68	0.8 (0.5, 1.2)

*Adjusted for age, education, personal smoking and study area.

Dietary factors

The diet of the subjects was dominated by staple grains (median intake among controls = 1,095 times per year), fresh vegetables (1,188 times per year), fermented salted foods (730 times per year), and soya bean products (365 times per year). Less frequent was consumption of animal protein sources (231 times per year), fresh fruits (52 times per year), and peas and beans (12 times per year). Risks of lung cancer in relation to dietary intake are shown in Table VIII. Higher frequencies of intake of vegetables, either those rich or low in carotene content were not significantly protective against lung cancer. The three foods with the highest carotene content in this study population were dried hot red peppers (16.9 mg of carotene per 100 g), dark leafy greens (2.7 mg of carotene per 100 g), and carrots (2.0 mg of carotene per 100 g). Carrots and dried hot red peppers were consumed less often by cases compared to controls, but these items were not frequently consumed (mean intake among controls was 41.4 and 70.0 times per year respectively). On the other hand, cases had slightly higher intakes of the more commonly consumed dark leafy greens (average intake among controls was 163.5 times per year).

Cases reported higher frequencies of intake of animal protein and fresh fruits. Few women (12% cases versus 8% controls) drank alcohol more than once a year, but they showed a significant smoking-adjusted 30% increased risk of lung cancer compared to those who did not drink at all. However, there was no clear trend with increasing alcohol consumption. There were no appreciable differences in dietary patterns for squamous/oat cell cancers versus adenocarcinoma, nor for smokers versus non-smokers.

Table VI Relative risk for lung cancer associated with previous lung diseases

	All lung		Squamous/oat		Adenocarcinoma	
	Cases/controls	RR* (95% CI)	N†	RR*	N†	RR*
Positive history of:						
chronic bronchitis and/or emphysema	210/137	1.4 (1.2, 1.8)	79	1.6‡	46	0.9
pneumonia	66/28	2.1 (1.3, 3.3)	23	2.3‡	15	1.6
tuberculosis	103/83	1.3 (0.9, 1.7)	33	1.2	33	1.1

*Adjusted for age, education, personal smoking and study area. †Number of cases with factor. ‡95% confidence intervals exclude 1.0.

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Table VIII Relative risk of lung cancer associated with dietary factors

Dietary factor	Intake (times per year)	Case/control	RR[a] (95% CI)
Staple grain	< 1095	308/266	1.0
	1095–1146	352/396	0.8 (0.7, 1.1)
	> 1146	290/290	0.9 (0.7, 1.2)
Peas and beans	< 4	256/241	1.0
	4–15	221/244	0.9 (0.7, 1.2)
	16–52	319/314	1.1 (0.8, 1.4)
	> 52	160/152	1.0 (0.7, 1.3)
Soya bean products	< 153	232/217	1.0
	153–365	204/266	0.7 (0.5, 0.9)
	366–485	265/250	0.9 (0.7, 1.2)
	> 485	255/219	1.0 (0.8, 1.3)
Animal protein	< 109	156/238	1.0
	109–230	229/236	1.6 (1.2, 2.1)
	231–442	235/237	1.6 (1.2, 2.1)
	> 442	336/241	2.3 (1.7, 3.0)
Fermented/salted foods	< 366	234/273	1.0
	366–625	179/154	1.2 (0.9, 1.6)
	626–990	329/306	1.2 (0.9, 1.5)
	> 990	214/219	0.9 (0.7, 1.2)
Vegetables[b] low in carotene content	< 366	254/251	1.0
	366–547	256/251	1.0 (0.8, 1.3)
	548–730	248/240	1.0 (0.8, 1.3)
	⩾ 731	198/210	0.8 (0.6, 1.1)
Vegetables[c] high in carotene content	< 731	201/223	1.0
	731–1095	355/331	1.1 (0.9, 1.4)
	1096–1460	195/197	1.0 (0.8, 1.3)
	⩾ 1461	205/201	0.9 (0.7, 1.2)
Fresh fruits	< 19	203/232	1.0
	19–52	209/249	1.0 (0.8, 1.3)
	53–132	256/231	1.4 (1.0, 1.8)
	> 132	288/240	1.5 (1.2, 2.0)
Alcohol beverages	0	649/706	1.0
	1–12	110/96	1.3 (0.9, 1.7)
	13–52	81/76	1.0 (0.7, 1.5)
	> 52	116/75	1.3 (1.0, 1.8)

[a]Adjusted for age, education, personal smoking and study area. [b]Includes white potato, pale sweet potato, white vegetables, yellow and green gourds. [c]Includes salted vegetables, dark sweet potato, yellow green squash, dark green leafy greens, yellow and light green leafy vegetables, carrots, red peppers, dried hot red peppers, green peas, tomatoes.

Multivariate analysis

The factors found to have a significant effect on risk of lung cancers in univariate analysis were evaluated simultaneously in multivariate unconditional logistic regression analysis. In addition to smoking, the following variables had a significant effect on risk of lung cancer ($P < 0.05$) and they entered the regression model in the order as shown: deep-frying, eye irritation, pneumonia, household tuberculosis, burning Kang, self-reported occupational exposure to burning fuel, passive smoking from any household member and heated brick wall/floor.

Discussion

This population-based case–control study conducted in two large northern Chinese cities revealed that at least 35% of the lung cancers among women can be explained by cigarette smoking. Although this attributable risk is low compared to Caucasian female populations (Lubin & Blot, 1984), it is higher than elsewhere in China (Chan *et al.*, 1979; Gao *et al.*, 1988), mainly because of a higher prevalence of smoking women in this region. Smoking rates among women over age 50 were nearly double those found in Shanghai or nationally in China (Gao *et al.*, 1988; Weng *et al.*, 1987). Furthermore, women in Harbin and Shenyang started to smoke at a relatively young age. As compared to women in Shanghai, where 19% of female smokers in the general population began smoking at age 19 or younger, approximately 40% started at this age in northern China. Hence, even though amounts smoked were low (averaging eight cigarettes per day among the cases), smoking contributes to the elevated rates of lung cancer among northern Chinese women. It also appears to account for the higher percentage (44%) of squamous/oat cell cancers in our study versus 32% and 35%, respectively, in Shanghai and Hong Kong (Gao *et al.*, 1988; Kung *et al.*, 1984). The relatively low mean daily number of cigarettes smoked by these women may explain the lower relative risks of lung cancer among Chinese compared to Caucasian smokers.

We observed no overall association between lung cancer risk and passive smoking. Our results varied by source of passive smoke exposure, however, with non-smoking cases reporting less exposure from spouses (but only in Harbin), more exposure from fathers, and similar exposure from mothers when compared to non-smoking controls. Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognised as a cause of lung cancer around the world (Surgeon General, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighbourhood air pollution (Xu *et al.*, 1989).

Pollution from coal burning seems likely to contribute to north-eastern China's elevated lung cancer rates. Risks increased with increasing years of use of burning Kang and heated brick walls/floors, and we observed weaker but similar trends with use of coal stoves and coal burners. Levels of air pollution have been reported to be high in both Harbin and Shenyang, with both indoor and outdoor wintertime benzopyrene concentrations exceeding standards for cities in the United States by more than 60-fold (Dai *et al.* personal communication; Xu *et al.*, 1989). Coal burning, especially use of a local smoky coal, has also been implicated in the high lung cancer rates reported among women in Xuan Wei County in southern China (Mumford *et al.*, 1987).

The effects of certain workplace exposures on lung cancer resemble those reported in Shanghai (Levin *et al.*, 1987, 1988), including a decreased risk seen in textile workers. The excess risk among women employed in metal smelting is consistent with the three-fold increased risk among men exposed to inorganic arsenic in copper smelting in Shenyang (Xu *et al.*, 1989) and the United States (Lubin *et al.*, 1981). The occupational findings will be presented in more detail in a separate report.

Our findings that cases were more likely to cook food by deep frying and to more frequently report eye irritation when they cooked are consistent with the increased risks associated with exposure to cooking oil fumes in Shanghai (Gao *et al.*, 1987). The association in Shanghai was strongest for use of rapeseed cooking oil, but few women in Harbin or Shenyang used this type of oil, suggesting that vapors from several types of cooking oils may be linked to increased risk. Condensates of both rapeseed and soya bean cooking oil volatiles have been found to be mutagenic (Qu *et al.*, 1986). Further short-term testing of several types of cooking oils is underway to help identify the responsible constituents and provide leads for additional study.

Certain lung diseases may have an aetiologic role in lung cancer development (Gao *et al.*, 1987; Wu *et al.*, 1988). Such an association is of particular importance in China, where the prevalence of chronic lung disease is high. Indeed we found that 35% of the cases and 24% of the controls reported prior chronic lung disease. Like others, we found an excess risk of squamous/oat cell cancers of the lung, but not adenocarcinoma, in association with chronic bronchitis/emphysema. Our finding of a significant increased risk associated with recent diagnosis of TB (i.e. 4–10 years prior to lung cancer) is consistent with results from Shanghai (Zheng *et al.*, 1988).

Our results are supportive of a familial tendency in lung cancers (Cohen *et al.*, 1977; Ooi *et al.*, 1986*a,b*; Skillrud *et al.*, 1987; Wu *et al.*, 1988). Shared environmental exposures, familial aggregation of smoking habits, and/or genetic predisposition may be important. The percentage of cases having

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affected first-degree family members was small (4%). Recent case-control studies in Great Britain (Ayesh *et al.*, 1984) and the United States (Caporaso *et al.*, 1989), however, suggest that genetic traits may influence susceptibility in a sizeable portion of cases. These investigations revealed significantly increased risks of lung cancer associated with the genetically controlled ability to extensively metabolise the drug debrisoquine, a trait affecting 54% of the control population studied in the United States.

We found no strong support for a role of hormonal factors for lung cancer overall or specifically for adenocarcinoma. The cases did tend to experience menopause at later ages, but the trend in risk with age at menopause was not smooth. History of prolonged labour or hysterectomy, which had been suspected as risk factors for adenocarcinoma because of the potential for trauma-associated lung embolism, occurred more frequently among our cases, but the excess risks were not significant since relatively few women were affected. Risk of lung cancer was recently reported to be increased among Chinese women with short menstrual cycle length (Gao *et al.*, 1988), but this variable was not assessed in the current study.

In other countries the risk of lung cancer is generally reduced among those with higher dietary intake of carotenoids (Ziegler, 1989), but our findings are less clear. Cases had slightly higher rather than lower intake of dark green leafy vegetables, the most commonly consumed rich source of carotene. Moreover, in our analysis using a combined index of all vegetables rich in carotene, high frequencies of intake did not confer a significant protective effect. Reasons for the absence of protective effects are not clear. A possible explanation is that three-fourths of the study population ate vegetables high in carotene content at least twice a day so that the nearly uniformly high intake of carotene-containing foods limited variability and hindered detection of an effect. Data on plasma carotene levels from this study population will be important as a more objective measure of their dietary intake. Misclassification of intake also may have dampened trends. We did not have information on portion size and the highest carotene-containing food in this population is dried hot red peppers, usually used as a condiment. In addition, recall of past diet may have been influenced by recent dietary improvements, perhaps more so among cases who may have been given preferential dietary treatment because of their illness.

In summary, this investigation revealed that contrary to a priori expectation in China, cigarette smoking is the major cause of lung cancer among women in north-east China and contributes to the area's high rates of mortality from this tumor. Prevention activities should emphasise smoking cessation, while additional study may help clarify the role of indoor and outdoor air pollution, chronic non-malignant lung disease, occupational exposures, familial susceptibility and other factors in the aetiology of lung cancer.

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Liu, Z., He, X. and Chapman, R.S., "Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China," International Journal of Epidemiology **20(1): 26-31, 1991.**

Lung cancer rates in Xuanwei County are among the highest in China. Previous studies (not epidemiologic) have suggested that there may be an association between burning smoky coal indoors and lung cancer incidence. This case-control study included 110 cases (56 males, 54 females) and 426 controls matched for age, sex, occupation (all were farmers), and village of residence (to control for type of fuel used). Only one of the female cases reported having ever smoked. Among men, the authors reported a statistically significant dose-response relationship with active smoking; however, of all the indices used to examine active smoking, only one category had a reported odds ratio that achieved statistical significance.

ETS exposure was assessed in women as whether there was at least one smoker (usually the husband) living in the same household. For 45 cases and 176 controls, an adjusted OR of 0.77 (95% CI 0.30-1.96) was reported.

Statistically significant increases in risk were reported for a number of other factors. In females, these were chronic bronchitis, OR = 7.37 (95% CI 2.40-22.66) and family history of lung cancer, OR = 4.18 (95% CI 1.61-10.85); in males, the associations were with chronic bronchitis, OR = 7.32 (95% CI 2.66-20.18), family history of lung cancer, OR = 3.79 (95% CI 1.70-8.42), and personal history of cooking food, OR = 3.36 (95% CI 1.27-8.88). Associations with lung cancer were also suggested for duration of cooking food and age at starting to cook for women (cooking takes place over coal-fired stoves).

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Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China

ZHIYUAN LIU*†, XINGZHOU HE* AND ROBERT S CHAPMAN**

Liu Z (Institute of Environmental Health and Engineering, Chinese Academy of Preventive Medicine, 29 Nan Wei Road, Beijing 10050, China), He X and Chapman R S. Smoking and other risk factors for lung cancer in Xuanwei, China. *International Journal of Epidemiology* 1991; 20: 26–31.

In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly-diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analysed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (odds ratio [OR] = 7.37, 95% confidence interval [CI]: 2.40–22.66) and family history of lung cancer (OR 4.18, 95% CI: 1.61–10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18 and 14.70), but not with passive smoking (OR 0.77, 95% CI: 0.30–1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% CI: 2.66–20.18), family history of lung cancer (OR 3.79, 95% CI: 1.70–8.42), and personal history of cooking food (OR 3.36, 95% CI: 1.27–8.88). In males a dose-response relationship of lung cancer with smoking index (years of smoking*amount of smoking) was shown by risks of 1.00, 2.61, 2.17 and 4.70.

Examination of Chinese nationwide cancer mortality statistics reveals that lung cancer mortality rates in Xuanwei County, Yunnan Province, are among the highest in China.[1] From 1973 through 1975, annualized male lung cancer death rates, age-adjusted to the 1964 China population, were 27.7 and 6.8 per 100 000 in Xuanwei and China, respectively. Corresponding mortalities in females were 25.3 and 3.2 per 100 000. Marked geographical variation in lung cancer mortality exists within Xuanwei. The county can be divided into high-, medium- and low-mortality areas, in which age-adjusted lung cancer mortalities in both sexes are 126.1, 20.9 and 6.0 per 100 000, respectively.

Xuanwei residents have traditionally burned three types of fuel, 'smoky' coal, 'smokeless' coal, and wood, for residential heating and cooking. Until the 1980s fuel was nearly always burned in an open, unventilated fire pit in the floor of the dwelling's main room; such fire pits are still widely used, though the use of ventilated stoves is increasing. Women have generally been responsible for starting and tending the domestic fire and cooking food, though men assume these responsibilities in some families.

Tobacco smoking is very rare in Xuanwei women, yet women's lung cancer rates are comparable to men's. Also, a survey of past fuel use showed that in the high-, medium- and low-mortality areas of Xuanwei, the percentages of families using smoky coal before 1958 were 87.6%, 60.1% and 6.1% respectively. Corresponding percentages of families using wood were 1.4%, 19.9% and 67.1%. Indoor concentrations of benzo(a)pyrene (BAP) averaged 627 ug/100 metres^3 (m^3) in the high-mortality area, and 46 ug/100 m^3 in the low-mortality area. In addition indoor pollution samples from the high-mortality area exhibited higher Ames-test mutagenicity than those from the low-mortality area.[2,3] All of these observations have served to suggest an association between indoor smoky coal burning and lung cancer in Xuanwei.

The case-control study reported here was designed to supplement existing information by assessing the influence of factors other than fuel type on the occurrence of lung cancer in Xuanwei. Such factors, includ-

*Institute of Environmental Health and Engineering, Chinese Academy of Preventive Medicine, 29 Nan Wei Road, Beijing 100050, China.
**US Environmental Protection Agency, Research Triangle Park, NC 27711 USA.
†Present address: Epidemiology Group, Biological and Medical Research Division, Argonne National Laboratory, Bldg. 203–J152, 9700 South Cass Avenue, Argonne, IL 60439 USA.

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ing tobacco smoking, family history of lung cancer, history of chronic bronchitis, and cooking habits, have been associated with lung cancer in areas other than Xuanwei, but their importance as contributors to lung cancer in Xuanwei has not yet been systematically determined. The present study also allowed comparison of the relative impact of these factors in males and females.

MATERIALS AND METHODS

In Xuanwei, 93.4% of the total population were farmers in 1982. Because of this, and because lung cancer mortality in Xuanwei farmers is high,[2] this study was confined to farmers. Concentrating the target population tended to increase the validity of the findings.[4] Between November 1985 and December 1986, we identified 112 cases of newly-diagnosed lung cancer at Xuanwei hospitals and clinics. After exclusion of two patients with unknown addresses, 110 lung cancer patients (56 males and 54 females) were included in data analysis. Of these, 19 (17%) had been diagnosed on the basis of cytological/pathological findings, and the remainder on the basis of clinical histories and X-rays.

Controls were selected to match lung cancer patients with respect to age (±2 years), sex, and village of residence. Because fuel use habits and dwelling types are similar within individual Xuanwei villages, this design was expected to provide effective matching with respect to indoor fuel type and dwelling type.

Such matching was sought because it would increase the effectiveness with which factors other than fuel type could be assessed. Cases and controls were matched on village, with as many eligible controls included as possible. Therefore, we selected more controls for each case in a large village than in a small village. The numbers of controls per case varied from one to five. After exclusion of 26 controls because of erroneous questionnaire responses, 426 controls were included in data analysis, an average of 3.87 controls per case. There were 9 cases with 1 control, 15 cases with 2 controls, 15 with 3 controls, 13 with 4 controls, and 58 with 5 controls.

A standardized questionnaire of the closed-question type was developed. Study factors included tobacco use history, family and personal medical history, domestic fuel use history, indoor fuel use history, personal history of cooking food, dwelling type, ethnic group (nationality), and socioeconomic and educational levels. After strict interviewer training and field testing, this questionnaire was administered directly to all lung cancer patients and controls. No interviewer or study subject knew the purpose of the study and hypotheses.

A summary index of tobacco smoking was developed for each subject. The smoking index was calculated by multiplying the duration of smoking (in years) by the amount of tobacco smoked (in kilograms per month). A subject was considered to have a positive family history of lung cancer if at least one relative was reported to have had the disease. The relatives included subjects' parents, siblings and children, and parents' siblings. A subject was considered to have a positive history of chronic bronchitis if he or she had been diagnosed by a doctor to have this condition, or reported cough for at least three months per year for at least two years before the year of interview. A female subject was considered to have been exposed to passive smoking if there was at least one smoker (mainly husband) who lived in the same household.

To assess the effects of individual independent variables, unmatched, unadjusted odds ratios (ORs) were calculated.[5] Confidence intervals were calculated using Miettinen's method.[6] Dose-response relationships were examined for variables related to smoking and cooking. Trends within these relationships were tested by extension of the Mantel-Haenszel procedure.[7]

To develop adjusted estimates of ORs associated with selected factors and interactions, conditional logistic regression models were also constructed for males and females.[8] In these models, all variables were dichotomous, assuming values of 0 or 1. The selected risk factors and interactions were treated as independent variables, and the presence or absence of lung cancer was treated as the dependent variable. These analyses were performed using the PECAN program.[9,10]

RESULTS

Distributions of characteristics in cases and controls are presented by gender in Table 1. Age, family size, ethnic group, birthplace, educational level, and dwelling type were comparable in cases and controls, so these factors were not considered further in data analysis. The effect of active tobacco smoking was not evaluated in females, since only one female (a control subject) had ever smoked tobacco. The village matching provided effective matching on fuel type because fuel-use habits (type and average amount) were similar in cases and controls.

Crude and adjusted ORs for smoking and cooking habits are presented with 95% confidence intervals for males in Table 2. No relationship between lung cancer and ever having smoked was observed. There was a suggestion of monotonic dose-response relationships of lung cancer with the age at which smoking began, duration of smoking and amount smoked by month.

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TABLE 1 *Comparison of lung cancer cases and controls, Xuanwei, China, 1985–1986*

Factor	Males		Females	
	Cases	Controls	Cases	Controls
Average age (years)	52	50	52	52
No. of people in family now	5.6	5.4	5.6	5.4
No. of people in family 20 years ago	5.8	5.5	5.9	5.5
Han nationality (%)	94.6	96.9	98.2	97.0
Born in Xuanwei (%)	100	100	100	98.0
Two-storey dwelling (%)	98.2	99.1	100	100
Amount of 'smoky' coal burnt (tons/year)	4.2	4.2	4.0	4.1
Amount of wood burnt (tons/year)	0.8	0.9	0.8	1.0

TABLE 2 *Odds ratios (OR) and 95% confidence intervals (CI) for lung cancer in males according to smoking and cooking, Xuanwei, China, 1985–1986*

Factor	Cases	Controls	ORc*	ORa**	95% CI
Ever-smoker					
No	4	19	1.00	1.00	
Yes	52	205	1.20	1.26	0.30– 5.26
Age of starting to smoke (years)					
Never	4	19	1.00	1.00	
>20	20	80	1.19	1.10	0.25– 4.93
≤20	32	125	1.22	1.39	0.32– 6.06
Trend (p value)			(p>0.05)		
Years of smoking					
0	4	19	1.00	1.00	
<35	30	146	0.98	1.07	0.25– 4.59
≥35	22	59	1.77	1.71	0.36– 8.12
Trend (p value)			(p>0.05)		
Amount of smoking (kg/per month)					
Never	4	19	1.00	1.00	
≤0.5	25	93	1.28	1.41	0.33– 6.09
0.6–1.0	20	93	1.02	1.09	0.24– 4.82
>1.0	7	19	1.75	1.91	0.32–11.40
Trend (p value)			(p>0.05)		
Smoking index†					
<2	4	30	1.00	1.00	
2–	24	99	1.82	2.61	0.69– 9.82
20–	16	74	1.62	2.17	0.55– 8.64
35–	12	21	4.28	4.70	1.03–21.40
Trend (p value)			(p<0.05)		
Often cooks food					
No	44	200	1.00	1.00	
Yes	12	24	2.27	3.36	1.27– 8.88

*ORc = Crude odds ratio.
**ORa = Odds ratio after adjustment by conditional logistic regression for other risk factors.
†Smoking index = Years of Smoking*Amount of smoking.

However, none of these relationships was statistically significant. In contrast, a statistically significant dose-response relationship of lung cancer with smoking index was observed. The adjusted OR in men who often cooked food (at least once a day) was 3.36 (95% CI: 1.27–8.88). The adjusted ORs were slightly larger than the crude ORs.

Crude and adjusted ORs for cooking and passive smoking are presented for females in Table 3. No dose-response relationship of lung cancer with age at which the woman began to cook food was observed, but the OR associated with the age at which the woman began to cook food (11–15 years old) was significant. Adjusted ORs associated with the duration of cooking were much larger than crude ORs. There was a suggestion of dose-response relationship of lung cancer with the duration of cooking food for the adjusted ORs. No relationship of lung cancer with passive smoking was observed.

Odds ratios for family history of lung cancer and personal history of chronic bronchitis were significantly associated with lung cancer in both sexes but duration of using an unventilated fire pit was not (Table 4). All conditional logistic regression ORs were larger than crude ORs in Table 4.

DISCUSSION

This study was intended to supplement previous studies which had shown a strong association of indoor smoky coal combustion with lung cancer in Xuanwei County.[2,3] Full understanding of lung cancer aetiology in Xuanwei, and comprehensive risk assessment of the effect of smoky coal use, require systematic assessment

TABLE 3 *Odds Ratios (OR) and 95% confidence intervals (CI) for lung cancer in females according to cooking and passive smoking, Xuanwei, China, 1985–1986*

Factor	Cases	Controls	ORc*	ORa**	95% CI
Age of starting to cook					
>15	13	73	1.00	1.00	
11–15	30	69	2.44	2.37	1.09– 5.15
≤10	11	60	1.03	1.25	0.45– 3.49
Trend (p value)			(p>0.05)		
Years of cooking					
≤30	7	53	1.00	1.00	
31–44	28	85	2.49	5.18	1.76– 47.49
≥45	19	64	2.25	14.70	1.61–134.03
Trend (p value)			(p>0.05)		
Passive smoking					
No	9	26	1.00	1.00	
Yes	45	176	0.74	0.77	0.30– 1.96

* ORc = Crude odds ratio.
** ORa = Odds ratio after adjustment by conditional logistic regression for other risk factors.

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TABLE 4 *Adjusted odds ratios (OR) and 95% confidence intervals (CI) for lung cancer in males and females, according to familial history of lung cancer, history of chronic bronchitis and years using unventilated fire pit, Xuanwei, China, 1985–1986*

Factor	Males			Females			Total		
	Case	Control	ORa* (95% CI)	Case	Control	ORa (95% CI)	Case	Control	ORa (95% CI)
Familial history of lung cancer									
No	41	200		45	192		86	392	
Yes	15	24	3.79 (1.70–8.42)	9	10	4.18 (1.61–10.85)	24	34	3.75 (2.05–6.83)
History of chronic bronchitis									
No	39	209		38	184		77	393	
Yes	17	15	7.32 (2.66–20.18)	16	18	7.37 (2.40–22.66)	33	33	7.61 (3.62–16.00)
Years using unventilated fire pit									
<45	22	107		21	84		43	191	
≥45	34	117	1.78 (0.46–6.93)	33	118	0.73 (0.20–2.60)	67	235	1.12 (0.46–2.74)

*ORa = Odds ratio after adjustment by conditional logistic regression for other risk factors.

not only of fuel use, but of other known and suspected risk factors as well. To achieve such an assessment, we chose a study design which provided effective case-control matching with respect to fuel type and average amount used as well as to age and gender.

Xuanwei is a very rural area. In the present study, almost all lung cancer patients were diagnosed by the county hospitals. Only 17% of the lung cancer cases were based on cytological/pathological findings, 83% were based on clinical histories and X-ray findings. Therefore, misclassification of the cases may exist in the study. However, other reasons may improve validity of lung cancer diagnosis in the study. Because of poor medical care in Xuanwei, most lung cancer patients had reached an advanced stage of the disease when diagnosed, and local doctors had wide experience of this diagnosis because of the high lung cancer morbidity in Xuanwei. In order to assess validity of the diagnosis, we also followed up a number of lung cancer patients from the study, almost all of whom died within six months of diagnosis.

In both males and females, the current study disclosed consistent and statistically significant associations of lung cancer with chronic bronchitis and positive family history of lung cancer. Lung cancer was also associated with the frequency of cooking food (in males) and the duration of cooking food (in females), even after the matching on fuel type inherent in the study design. Not surprisingly, lung cancer was associated with active smoking in males. No association with passive smoking was observed in females.

In Xuanwei, women are generally responsible for cooking food, so the variable 'cooks or does not cook food' could not be assessed in females. However, the ORs associated with the variable 'years of cooking' suggested that lung cancer risk increased with increase in duration of cooking (Table 3). There was no dose-response relationship between lung cancer and age at which a woman began to cook food. This observation may be due to the possibility that women who reported cooking food at less than ten years old did not really cook food at that age. The OR in males who often cooked food was over three times greater than in those who did not. It is likely that those who cook food inhale more coal-smoke pollution than those who do not. Wu *et al* reported that subjects exposed to burning coal used for heating or cooking in a stove or fireplace during the majority of childhood and the teenage years had a lung cancer risk 2.3 times higher than subjects who were not so exposed.[11] Wang *et al* have reported similar results from China.[12] Gao *et al* reported increased risk of lung cancer in Shanghai women who cook frequently with rapeseed oil.[13] This observation raises the question of whether pollutants associated not only with the cooking fuel but also with the cooking method promote lung cancer.

The observed association of lung cancer with positive family history of the illness may be attributable in part to recall bias. However, our results are consistent with other studies[14–17] which tends to reinforce the validity of the association. Our relative risk estimates for positive family history of lung cancer, 3.79 in males and 4.18 in females, were also similar to previous studies. The association may be due partly to the fact that a subject's relatives lived in the same environment as the subject for some time. Mulvihill has postulated that some abnormal types of gene might increase sensitivity to environmental carcinogens.[18] Further research will be necessary to elucidate and distinguish the roles of genetic and environmental factors in carcinogenesis.

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Tobacco smoking is generally accepted to be a major cause of lung cancer.[19–22] We observed an association of lung cancer with tobacco smoking in males, and this observation tended to enhance confidence in the results. However, the association was weaker than has been reported in many previous studies.[13,19] When considered individually, duration of smoking, amount of smoking, and age at which smoking began were only weakly associated with the illness. Only the smoking index derived by multiplying duration by amount of smoking was significantly associated with lung cancer.

These observations may be due partly to the fact that only 23 (8.2%) of 280 males in this study were lifetime non-smokers. In such a small comparison group, even fairly small changes in the distribution of non-smokers between cases and controls could have produced marked differences in observed ORs associated with smoking. More importantly many farmers in Xuanwei smoke tobacco through a long bamboo cylinder partly filled with water and the passage of smoke through the water may filter out carcinogenic substances. Studies comparing the composition of water-filtered to unfiltered tobacco smoke are currently in progress.

It is also quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking. For example, as mentioned above, the average indoor concentration of BAP in the Xuanwei region of high lung cancer mortality was 627 ug/100 m^3 in a recent survey. An individual inhaling 12 m^3 of air per day might therefore inhale 9154 ug of BAP in a year if he or she spent eight hours per day indoors. In contrast, an individual smoking 20 cigarettes per day might be expected to inhale only about 700 ug of BAP in one year.[23] Thus, it is not especially surprising that the ORs associated with smoking in Xuanwei males were smaller than reported in other studies. Because unusual environmental conditions prevail in Xuanwei, it would not be advisable to generalize these ORs to other areas.

Smoking is very rare in Xuanwei females. In addition, we observed no association of lung cancer with passive smoking in females. Such an association has been reported in several previous investigations.[24–27] In non-smoking women in Shanghai, Gao *et al* observed a limited association of lung cancer with passive smoking; in that study the relative risk ranged from 1.0 in women living less than 20 years with a smoking husband to 1.7 in those living with a smoking husband for at least 40 years.[25] However Koo *et al* have not observed a consistent association of lung cancer with passive smoking in Chinese women.[28–30] These authors also stated that correlates of passive smoking such as diet and socioeconomic status can act as important confounders when the health risks of passive smoking are evaluated.[31] The heavy indoor air pollution in Xuanwei may also overwhelm the carcinogenic effect of passive smoking. The effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region may therefore not be applicable to other regions.

In summary, this study was undertaken to supplement existing evidence showing a strong association of lung cancer with indoor use of smoky coal in Xuanwei. Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that these factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei. A separate case-control study, which will allow simultaneous direct analysis of the effects of indoor air pollution and other known and suspected lung cancer risk factors in Xuanwei, is currently in progress.

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OTHER STUDIES DISCUSSING LUNG CANCER

In addition to the primary lung cancer studies discussed in Section A of this notebook, there are several other studies which are sometimes mentioned in the context of epidemiologic studies on ETS and lung cancer. Because these studies are methodologically flawed or report incomplete data, they are of limited usefulness. For instance, the earlier studies (e.g., Knoth, et al., 1983; Miller, 1984; Sandler, et al., 1985) were excluded from the Letzel and Überla meta-analysis (1990), and even from the meta-analyses conducted by the National Academy of Sciences in 1986 and by the Environmental Protection Agency in 1990.

Following are brief summaries of each of these studies, focusing on their problems. Copies of these studies follow this introduction, arranged in chronological order and highlighted in yellow for useful information and in blue for adverse information.

Knoth, et al., 1983.

- This German study included a total of 792 lung cancer patients. There was no control population for comparison, and thus, the authors' conclusions are of limited value.[1]

- One reviewer commented that this report contained "only tentative conclusions based on poor data analyzed by

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unacceptable methods."[2]

Sandler, et al., 1985

- Although the papers published by Sandler, et al., in 1985 focused on overall mortality, some numbers of lung cancer deaths were presented.[3]

- The methodology and interpretation of these studies have been heavily criticized (e.g., one scientist described the studies as "heavily flawed").[4] The data presented are of limited value.

Dalager, et al., 1986.

- Data from three case-control studies conducted in the United States under the auspices of the National Cancer Institute were combined and analyzed in this study.[5] (Two of the studies, Correa, et al., and Buffler, et al., were discussed in Section A of this notebook.)

- Because the Dalager paper includes two primary studies on ETS and lung cancer, if it were included in considerations of the epidemiologic studies, it would result in some data being "counted" twice.

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Lloyd, et al., 1986.

- In a study investigating the high rate of lung cancer in one town in Scotland, relatives of 42 cases who had died of lung cancer and of 42 matched controls who had died of other causes were interviewed.[6]

- Conclusions about ETS exposure were based on smokers and nonsmokers combined, thus precluding comparisons to the primary studies cited in Section A of this notebook. However, the authors reported no statistically significant differences between cases and controls for any questions relative to personal smoking or to ETS.

Katada, et al., 1988.

- This study, using hospitalized individuals in Nara, Japan, included only 25 female lung cancer cases (some of whom were smokers) and 50 female controls.[7]

- All of the cases reported present exposure to ETS, all but two reported past exposure, and all but four reported childhood exposure. Thus, the reference categories (i.e., non-exposed women) are too small to allow appropriate calculations of relative risk.

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- Nevertheless, none of the case-control comparisons was statistically significant at the 5% level. (Note: the paper also bases some of its conclusions on nonsmokers and smokers combined.)

Lam and Cheng, 1988

- This paper reviews four lung cancer studies previously conducted in Hong Kong, all of which are presented in the Primary Studies section of this notebook.[8]

- Using meta-analysis, Lam and Cheng calculate a statistically significant summary point estimate for the four studies.

Chen, et al., 1990

- In 1990, conclusions based on a study of 332 cases and 635 group-matched hospital controls in Taiwan were published.[9]

- For ETS exposure, point estimates achieving statistical significance were reported; however, it appears that these point estimates were calculated using <u>both</u> nonsmokers <u>and</u> active smokers, and are thus not comparable with other studies of nonsmokers only.

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Miller, 1990.

- Miller used newspaper death notices to ascertain cancer deaths in women in northwestern Pennsylvania, and then interviewed surviving next-of-kin to obtain information on the deceased women. This approach could be expected to result in problems related to accurate recall by those interviewed.[10]

- In a 1984 paper, Miller examined "all cancer deaths" (See Other Cancers section in this notebook); in the 1990 paper, he provides numbers of cancer deaths by site.

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PASSIVE SMOKING AS A CAUSATIVE FACTOR OF LUNG CANCER IN NONSMOKING WOMEN

by

A. Knoth, H. Bohn and F. Schmidt

of

Preventive Oncology Research Institute,
Mannheim Faculty of Clinical Medicine,
University of Heidelberg,
Mannheim, West Germany

from

Med. Klin. Prax. 78(2), 56-59 (1983)

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PASSIVE SMOKING AS A CAUSATIVE FACTOR OF LUNG CANCER IN NONSMOKING WOMEN

by

A. Knoth, H. Bohn and F. Schmidt

ABSTRACT:

In a study on 792 patients with bronchogenic carcinoma of both sexes in the region Mannheim-Ludwigshafen-Heidelberg 59 female bronchogenic carcinomas were found. 39 of them appeared in non-smoking female patients. 61,5% of them had lived in domestic community with smokers. This is nearly the threefold as could be expected on the basis of smoking behavior of men in the respective groups of age. Suggestions on professional exposition to cancerogenic substances could not be found just as little as references to hereditary factors. Passive smoking is by far the obvious interpretation for the high share of non-smokers in our female patients with bronchogenic carcinoma the more so since the percentage of squamous cell and small-cell carcinomas which are valid as typical carcinomas of smokers, did not lie essentially lower in our non-smoking wives (66,6%) in comparison to female smokers (80%). As a further support of this interpretation is refered to similar results in the world literature proving our findings as not surprising.

In a study on 792 lung cancer patients published in a previous paper (Med. Klin. Prax., 1/1983) we had investigated the question of whether "light smoking" (smoking of filter-tipped cigarettes) reduces the lung cancer risk, and had found at least five indicators to refute this hypothesis. However, we also came upon another significant finding which called for further analysis: while 97.3% of the 733 male patients with bronchial carcinomas were smokers, there were 39 nonsmokers among the 59 women with lung cancer, i.e., more than half the female patients. As it was not possible to demonstrate any evidence of special occupational exposure to carcinogens either in the men with lung cancer or in the women -- 47.1% of the women with bronchial carcinomas, being housewives, had no occupation whatsoever, 23.5% were unskilled working women and

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17.6% were office workers -- the question arose of what other harmful agents could be considered as being responsible for the especially high percentage of nonsmoking women among our female patients. The fact that general air pollutants play a secondary role as a causative agent of bronchial cancer as well has been shown again just recently by Ulmer [15] in a meticulous study from Northrhine-Westfalia.

Concerning the methods, we refer to our previous publication [5]. Hereditary factors were ruled out already because the great increase in the incidence of bronchial carcinoma in women as well would require a radical change in the hereditary composition in numerous countries in the past decades. Nor is there any indication of such a change [12].

In view of the sensational findings of Hirayama [4] and Trichopoulos et al. [14], we focused our attention primarily on the smoking habits of the husbands and other family members living in the same household with the nonsmoking female lung cancer patients.

A comprehensive review of passive smoking and cancer had been published by Schmidt in MEDIZINISCHE KLINIK in 1979 [9]. In that review he listed, inter alia, more than 40 carcinogenic substances which had been detected in tobacco smoke.

Especially High Carcinogen Level in Sidestream Smoke

The possibility of a cancer-causing effect not only of active smoking but also of passive smoking can no longer be challenged with scientific arguments for the following reasons:

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1. The overwhelming majority of the above-mentioned more than 40 carcinogenic substances present in tobacco smoke enter the surrounding air with the sidestream smoke, and thus the passive smoker is forced to inhale them as well. The sidestream smoke does not differ qualitatively, but only quantitatively from the mainstream smoke which is inhaled by the smoker himself when puffing on the cigarette. Consequently, the health hazard of passive smoking is directly related to the health hazards of the smoker proper. The severe health damage which the "active" smoker must expect makes it ab initio very unlikely for passive smoking to be merely a nuisance. Even though the passive smoker inhales the tobacco smoke in more or less dilute form, the significance of this dilution factor is rendered relative by the fact that the level of the carcinogens among the harmful substances is much higher in the sidestream smoke than in the mainsteam which is inhaled only by the smoker himself.

2. The carcinogenic effect of passive smoking has been clearly established in animal experiments. Ca. 10% of the golden hamsters used developed laryngeal carcinomas even in the experiment designed in the Forschungsinstitut der Deutschen Zigarettenindustrie [Research Institute of the West German Cigarette Industry], and the corresponding percentage was even higher, 20% in a U. S. study. It was possible to increase the lung tumor incidence by passive smoking to 91% in some cases in predisposed mouse strains (reference in [9]).

3. The more than a dozen nitrosamines detected in tobacco smoke deserve particular attention in this respect both qualitatively and quantitatively. One ppm (= parts per million) of them is already

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considered to be potentially carcinogenic. All animal species investigated so far (more than 20) responded to nitrosamine by tumor development without exception. Therefore, we must assume that nitrosamines induce cancer in humans as well.

It is also of particular significance that the nitrosamine level in tobacco smoke is so high that smoking must be considered to be the most important source of exogenous nitrosamine in the environment in general. The situation is further aggravated by the circumstance that according to Brunnemann et al. [1,2], the nitrosamine level in the sidestream smoke is up to 50 times higher than in the mainstream smoke which is inhaled only by the smoker. This especially strongly increased nitrosamine level in the sidestream smoke renders the dilution effect so strongly relative that -- according to the same authors -- the nitrosamine uptake by passive smokers in rooms filled with smoke can reach levels which correspond to the nitrosamine content in the mainstream smoke of up to 30 cigarettes per hour! The nitrosamine level in the sidestream smoke of tobacco is, for example, at least 1,000 times higher than in beer or in aminophenazone, an otherwise good medicine, which was withdrawn from circulation because of minute traces of nitrosamine, or than the maximum values which have been specified recently in the nitrosamine ordinance for pacifiers for babies.

There is No Harmless Dose

4. Carcinogens are distinguished from other toxic substances by their pronounced summation effect. The individual partial doses add up to a critical threshold value beyond which cancer usually

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becomes clinically manifest. Even very small doses -- one millionth of one gram -- produce irreversible changes in the cell (= tumor blastoderm). Therefore, in principle, there is no fully harmless dose for carcinogenic substances, because the possibility cannot be ruled out that the partial doses inhaled by passive smoking lead to levels exceeding the carcinogenic threshold value which perhaps would not have been reached otherwise during the life of the patient by summation with other carcinogens present in the environment which none of us can fully escape, and thus cancer becomes clinically manifest during the lifetime. For the same reason, there are no MAC [Maximum Allowable Concentrations] for carcinogenic substances either.

5. Based on these facts the present epidemiological findings are by no means surprising. Hirayama's study [4] on more than 91,000 nonsmoking married Japanese women above the age of 40 years should be mentioned in particular in this connection. According to this study, nonsmoking women married to smokers had more than double the lung cancer incidence of women married to nonsmokers. He also found a statistically significant relationship between the lung cancer risk of the nonsmoking women and the intensity of smoking of the spouses, but no such relationship for other forms of cancer (gastric and endometrial cancers).

Similar findings were also obtained by Trichopoulos et al. [14] in Athens by a totally different methodological approach: When comparing the smoking habits of the husbands of 51 women with lung cancer with those of 163 women with other diseases, the lung cancer incidence of nonsmoking women married to smokers was found to increase, on an average,

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by a factor of 2.4, and even by a factor of 3.4 when the husband smoked more than two packs of cigarettes a day.

In a subsequent evaluation of the materials of the prospective study of the American Cancer Society on the pattern of Hirayama's study [4], Garfinkel [3] also found at least a similar tendency, even though it was not possible to demonstrate any statistical significance: When taking the age-adjusted lung cancer incidence in nonsmoking wives of nonsmokers for 1, the figure rose to 1.37 when the nonsmoking women were married to smokers who smoked more than 20 cigarettes a day.

These findings of Garfinkel, which show the same trend as Hirayama's studies, could be plausibly explained when considering the following circumstances: The rooms in Japanese wooden houses, especially in the country, are known to be very small and have low ceilings. Harmful concentrations are reached within a short time due to the small air volume; in agreement herewith the risk for nonsmoking women in the country was especially high. American homes are, however, not only more spacious and the rooms generally bigger, but a higher percentage of them are also air-conditioned. As the homes are bigger, the nonsmoking women in the United States also have more possibility to withdraw to other rooms when they feel excessively bothered by the smoking of their husbands, aside from the tobacco smoke concentration being also generally lower.

Unproportionately High Percentage of Nonsmoking Women with Bronchial Carcinoma Live with Smoking Men

61.5% of the 39 nonsmoking women with bronchial carcinomas in our study lived in the same household with smoking men. This percentage

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is far higher than was to be expected based on the percentage of smoking men in the age groups being considered.

The data on the smoking habits were obtained from the family members themselves, usually from the husband, in this study as well. As it was quasi in the interest of these subjects to supply data, they can be assumed to be especially reliable.

According to the recent "microcensus" of the Statistisches Bundesamt [Bureau of Statistics of West Germany] covering 2 million citizens [13], 38.6% of the men were smokers. The majority is accounted for by younger smokers in the age group of 20-40 years. Only 22.4% of the men were smokers in the age bracket 50-69 years, i.e., in the age group which includes most of the husbands of our nonsmoking female patients [6]. When taking this into account, twice or even three times as many of the nonsmoking women with bronchial carcinoma lived together with smoking men than was to be expected statistically, which remarkably duplicates Hirayama's [4] findings in Japan and Trichopoulos' [14] findings in Athens.

The fact that 66.6% of the bronchial carcinomas in the nonsmoking married women were squamous epithelial and small-cell carcinomas is also indicative of the involvement of passive smoking in the development of cancer, because the corresponding percentage was not substantially higher among the smoking women (80%). Since -- as was mentioned before -- occupational exposure to carcinogens and hereditary factors as the cause of the increased incidence of bronchial carcinoma in nonsmoking female patients are ruled out, it could hardly be disputed that the causal involvement of passive smoking in the bronchial carcinomas of the

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nonsmoking married women is by far the most plausible explanation in our study as well.

Sufficient Evidence of Health Hazard

It was demonstrated by Schmidt elsewhere that passive smoking -- completely regardless of a possible carcinogenic effect -- is a true health risk [7,8,10,11]. The exaggerated criticism of the results, especially of Hirayama [4], must therefore be opposed all the more emphatically: The cigarette industry even attempted to make these findings appear incredible in full-page ads in leading newspapers in West Germany. The chief witnesses were, without exception, members of the Forschungsrat Rauchen und Gesundheit der Zigarettenindustrie [Research Council on Smoking and Health of the Cigarette Industry] which distributed 20 million DM made available by the industry for research purposes during the past years without making it public. The inglorious role played by this "Research Council" has already been exposed by one of us elsewhere [10] in detail. With good reason this can be described as no less a scandal than the exposure of the "Neue Heimat". Therefore, the Medical Task Force on Smoking and Health passed the following resolution in its 1981 annual general meeting in Berlin:

"The cigarette industry is increasingly misusing the so-called Research Council on Smoking and Health sponsored by it to manipulate public opinion regarding the question of passive smoking. Therefore, we regard the direct sponsorship of research on the problems of smoking by the cigarette industry and the financial grants, e.g., even to medical journals, bypassing established research institutions, such as the

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Deutsche Forschungsgemeinschaft [West German Research Association], as a serious threat to scientific freedom which comes alarmingly close to disguised corruption. Therefore, we urge the West German Federal Minister for Science to guarantee, as a minimum, at least the disclosure by the cigarette industry of how these millions granted for 'promoting research' on smoking are used. In addition, the name of the sponsor should be indicated in all publications of independent institutes on the problem of smoking, which were sponsored by the cigarette industry."

We are pleased to report that von Bülow, West German Federal Minister for Research, has informed the Medical Task Force on Smoking and Health on January 27, 1982 that he considered our demands to be justified -- and not only in this special case -- and that he would take them into account in his further discussions with prof. Schmähl. It is also shameful that leading members of the board of directors of Deutsche Gesellschaft für Arbeitsmedizin [West German Society for Industrial Medicine], e.g., G. Lehnert and H. Valentin, being heavy smokers themselves, do not shrink from turning all principles of preventive medicine upside down and considering passive smoking only as a nuisance until proof of the health hazard, which should be watertight in every respect, is available. According to the principles of preventive medicine, any harmful agent whose health hazards can be supported with an impressive wealth of data as in the case of tobacco smoke in general, should be considered hazardous for health even when diluted until the opposite, i.e., the harmlessness of passive smoking, is proved.

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A. Knoth, H. Bohn, F. Schmidt:
Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen
Med. Klin. Prax. 78 (1983), Nr. 2

A. Knoth, H. Bohn, F. Schmidt
Forschungsstelle für präventive Onkologie
(Leiter: Prof. Dr. F. Schmidt),
Klinische Fakultät Mannheim der Universität Heidelberg

Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen

Zusammenfassung

In einer Studie an 792 Bronchialkarzinompatienten beiderlei Geschlechts aus dem Raum Mannheim–Ludwigshafen–Heidelberg wurden unter 59 Lungenkrebspatientinnen 39 Nichtraucherinnen gefunden. 61,5% von ihnen hatten in häuslicher Gemeinschaft mit Rauchern gelebt. Das ist nahezu das Dreifache von dem, was aufgrund der Rauchgewohnheiten der Männer in den betreffenden Altersgruppen zu erwarten war. Da Hinweise auf berufliche Kanzerogenexposition ebensowenig ermittelt werden konnten wie erbliche Faktoren, wird das Passivrauchen für den hohen Anteil an Nichtraucherinnen bei unseren Bronchialkarzinompatientinnen als die mit Abstand naheliegendste Erklärung betrachtet, zumal der Anteil an Plattenepithel- und kleinzelligen Karzinomen, die als typische Raucherkrebse gelten, mit 66,6% gegenüber 80% bei den Raucherinnen nicht wesentlich niedriger lag. Als weitere Stütze dieser Interpretation wird auf ähnliche Befunde in der Literatur hingewiesen, die dieses Ergebnis keineswegs als überraschend erscheinen lassen.

In einem vorangegangenen Beitrag (Med. Klin. Prax. 1/1983) waren wir in einer Studie an 792 Lungenkrebspatienten der Frage nachgegangen, ob „Leichtrauchen" (Rauchen von Filterzigaretten) das Lungenkrebsrisiko vermindert, und hatten mindestens fünf Indizien dafür gefunden, daß dies nicht der Fall ist. Dabei stießen wir jedoch auf einen weiteren bedeutsamen Befund, der eine nähere Analyse erforderlich machte: Während 97,3% der 733 männlichen Bronchialkarzinompatienten Raucher waren, fanden sich unter 59 Frauen mit Lungenkrebs 39 Nichtraucherinnen, also mehr als die Hälfte. Da wir Hinweise auf besondere berufliche Kanzerogenexposition weder bei den Männern mit Lungenkrebs noch bei den Frauen ermitteln konnten – 47,1% der Bronchialkarzinompatientinnen übten als Hausfrauen überhaupt keinen Beruf aus, 23,5% waren in ungelernten Berufen tätig und 17,6% waren Angestellte –, ergab sich die Frage, welche weiteren Noxen für den besonders hohen Anteil von Nichtraucherinnen in unserem weiblichen Patientengut in Frage kamen. Daß allgemeine Luftverunreinigungen als Bronchialkrebsursache allenfalls eine Nebenrolle spielen, hat im übrigen Ulmer [15] soeben erneut in einer sorgfältigen Studie aus Nordrhein-Westfalen gezeigt.

Hinsichtlich der Methodik verweisen wir auf unsere frühere Publikation [5]. Erbfaktoren schieden schon allein deshalb aus, weil der starke Anstieg des Bronchialkarzinoms auch bei Frauen eine gravierende Änderung der erblichen Zusammensetzung in zahlreichen Ländern in den letzten Jahrzehnten erfordern würde. Auch dafür liegt kein Anhaltspunkt vor [12].

Im Hinblick auf die aufsehenerregenden Befunde von Hirayama [4] und Trichopoulos et al. [14] wandten wir deshalb unsere besondere Aufmerksamkeit den Rauchgewohnheiten der Ehegatten und anderer in häuslicher Gemeinschaft mit den nichtrauchenden Lungenkrebspatientinnen lebender Angehöriger zu.

Schon 1979 veröffentlichte Schmidt in der MEDIZINISCHEN KLINIK eine umfassende Übersicht über Zwangsrauchen und Krebs [9]. In dieser Übersicht stellte er unter anderem mehr als 40 krebserzeugende Stoffe tabellarisch zusammen, die bisher im Tabakrauch nachgewiesen wurden.

Kanzerogengehalt im Nebenstromrauch besonders hoch

Die Möglichkeit einer krebserzeugenden Wirkung nicht nur des Aktiv-, sondern auch des Passivrauchens läßt sich aus folgenden Gründen mit wissenschaftlichen Argumenten nicht mehr bestreiten:

1. Der größte Teil der erwähnten über 40 krebserzeugenden Stoffe des Tabakrauches geht mit dem Nebenstrom in die Umgebungsluft, wo ihn zwangsläufig auch der Passivraucher einatmen muß. Der Nebenstromrauch unterscheidet sich vom Hauptstromrauch, den der Raucher selbst beim Ziehen an der Zigarette inhaliert, nicht qualitativ, sondern lediglich quantitativ. Das Gesundheitsrisiko des Passivrauchens steht demnach in unmittelbarer Beziehung zu den Gesundheitsgefahren des Rauchens

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A. Knoth, H. Bohn, F. Schmidt
Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen
Med. Klin. Prax. 78 (1983), Nr. 2

ten einleuchtend erklärt werden: Die Wohnräume in den japanischen Holzhäuschen, speziell auf dem Land, sind bekanntlich sehr klein und niedrig. Durch ihr geringes Luftvolumen werden hier bedenkliche Konzentrationen schon nach kurzer Zeit erreicht; in Übereinstimmung damit war die Gefährdung der nichtrauchenden Ehefrauen auf dem Land besonders hoch. Die amerikanischen Wohnungen sind dagegen nicht nur geräumiger und die Zimmer im Durchschnitt größer, sondern auch in einem hohen Prozentsatz klimatisiert. Durch die größeren Wohnungen hat zudem eine nichtrauchende Ehefrau in den USA, die sich durch das Rauchen ihres Gatten zu stark belästigt fühlt, neben der ohnehin geringeren Tabakrauchkonzentration auch noch eher die Möglichkeit, in andere Wohnräume auszuweichen.

Nichtrauchende Bronchialkrebspatientinnen leben überproportional häufig mit Rauchern zusammen

Von den 39 nichtrauchenden Bronchialkarzinompatientinnen unserer Studie hatten 61,5% in häuslicher Gemeinschaft mit Rauchern gelebt. Das ist weit mehr, als aufgrund des Anteils rauchender Männer in den in Betracht kommenden Altersgruppen zu erwarten war.

Die Angaben über die Rauchgewohnheiten stammten auch hier von den Familienangehörigen selbst, in der Regel vom Ehemann. Da sie quasi in eigener Sache gegeben wurden, darf man annehmen, daß diese Angaben besonders zuverlässig sind.

Nach dem letzten Mikrozensus des Statistischen Bundesamtes an zwei Millionen Bundesbürgern [13] rauchten 38,6% der Männer. Den Hauptanteil stellen dabei die jüngeren Raucher in der Altersgruppe von 20 bis 40 Jahren. Im Alter von 50 bis 69 Jahren – der Altersgruppe, die vorzugsweise als Ehemänner für unsere Patientinnen in Betracht kommt – rauchten sogar nur noch 22,4% der Männer [6].

Stellt man dies in Rechnung, lebten von den nichtrauchenden Bronchialkarzinompatientinnen doppelt oder sogar dreimal so viele mit Rauchern in häuslicher Gemeinschaft, als statistisch zu erwarten war – eine bemerkenswerte Parallele zu den Befunden von Hirayama [4] in Japan und Trichopoulos [14] in Athen.

Für die Beteiligung des Passivrauchens an der Krebsentstehung spricht in unserer Studie auch, daß 66,6% der Bronchialkarzinome bei den nichtrauchenden Ehefrauen Plattenepithel- und kleinzellige Karzinome waren; bei den Raucherinnen waren es mit 80% nicht wesentlich mehr. Da – wie schon erwähnt – berufliche Kanzerogenexposition und Erbfaktoren als Ursachen für das gehäufte Auftreten von Bronchialkrebs bei nichtrauchenden Patientinnen ausscheiden, dürfte kaum zu leugnen sein:

Eine ursächliche Beteiligung des Passivrauchens an den Bronchialkarzinomen der nichtrauchenden Ehefrauen auch unserer Studie ist die mit Abstand einleuchtendste Erklärung.

Gesundheitsschädlichkeit ausreichend bewiesen

An anderer Stelle wurde von Schmidt nachgewiesen, daß das Passivrauchen – völlig unabhängig von einer eventuell krebserzeugenden Wirkung – ein echtes Gesundheitsrisiko darstellt [7, 8, 10, 11]. Mit um so größerem Nachdruck muß deshalb der überspitzten Kritik an den Ergebnissen besonders von Hirayama [4] entgegengetreten werden: Die Zigarettenindustrie versuchte sogar durch ganzseitige Anzeigen in führenden Tageszeitungen der Bundesrepublik Deutschland diese Befunde als unglaubwürdig hinzustellen. Kronzeugen waren dabei ausnahmslos Mitglieder des Forschungsrates Rauchen und Gesundheit der Zigarettenindustrie, der in den letzten Jahren – ohne Offenlegung – 20 Millionen DM an Forschungsmitteln verteilte, die von der Industrie zur Verfügung gestellt wurden. Auf die unrühmliche Rolle dieses „Forschungsrates" ist einer von uns an anderer Stelle [10] im Detail eingegangen. Mit guten Gründen kann man dies als einen nicht minder großen Skandal bezeichnen wie die Enthüllungen um die „Neue Heimat". Schon 1981 verabschiedete deshalb der Ärztliche Arbeitskreis Rauchen und Gesundheit auf seiner Jahreshauptversammlung in Berlin dazu folgende Resolution:

„Die Zigarettenindustrie mißbraucht den von ihr finanzierten, sogenannten Forschungsrat Rauchen und Gesundheit mehr und mehr dazu, die öffentliche Meinung in der Frage des Passivrauchens zu manipulieren. Wir erblicken deshalb in der direkten Forschungsförderung zur Problematik des Rauchens durch die Zigarettenindustrie und in finanziellen Zuwendungen, z.B. auch an medizinische Zeitschriften, unter Umgehung bewährter Forschungseinrichtungen wie der Deutschen Forschungsgemeinschaft, eine ernsthafte Bedrohung der Freiheit der Wissenschaft, die einer getarnten Korruption bedenklich nahekommt. Wir fordern deshalb den Bundeswissenschaftsminister auf, als Minimum eine Offenlegung der Verwendung dieser Millionenbeträge zur ‚Forschungsförderung' über das Rauchen durch die Zigarettenindustrie sicherzustellen. Ferner ist für alle Veröffentlichungen unabhängiger Institute zur Problematik des Rauchens, die durch die Zigarettenindustrie gefördert wurden, ein Hinweis auf den Geldgeber zu fordern."

Erfreulicherweise teilte Bundesforschungsminister von Bülow dem Ärzt-

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A. Knuth, H. Bohn, F. Schmidt
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heitsschäden, mit denen der „aktive" Raucher rechnen muß, machen es von vornherein höchst unwahrscheinlich, daß das Zwangsrauchen nur eine Belästigung sein sollte. Zwar inhaliert der Passivraucher den Tabakrauch mehr oder weniger verdünnt; die Bedeutung dieses Verdünnungsfaktors wird jedoch schon dadurch wesentlich relativiert, daß der Schadstoffgehalt des Nebenstromrauches gerade an Kanzerogenen viel höher ist als der Gehalt im Hauptstrom, den nur der Raucher selbst einatmet.

2. Im Tierexperiment ist die kanzerogene Wirkung des Passivrauchens eindeutig gesichert. Sogar im Forschungsinstitut der Deutschen Zigarettenindustrie selbst entwickelten etwa 10% der verwendeten Goldhamster Kehlkopfkarzinome; nach einer US-Studie waren es sogar 20%. Die Lungentumorrate konnte in disponierten Mäusestämmen durch Passivrauchen zum Teil bis auf 91% gesteigert werden (Literatur bei [9]).

3. Besondere Beachtung verdienen in diesem Zusammenhang die mehr als ein Dutzend im Tabakrauch nachgewiesenen Nitrosamine sowohl in qualitativer als auch in quantitativer Hinsicht. Ein 1 ppm (= pars per million) davon gilt bereits als potentiell kanzerogen. Alle – mehr als 20 – bisher untersuchten Tierarten reagierten auf Nitrosamine ausnahmslos mit Tumorbildung. Wir müssen deshalb annehmen, daß Nitrosamine auch beim Menschen Krebs erzeugen.

Von besonderer Bedeutung ist weiterhin, daß gerade der Nitrosamingehalt im Tabakrauch so hoch ist, daß das Rauchen als die wichtigste exogene Nitrosaminquelle in unserer Umwelt überhaupt gelten muß. Erschwerend fällt dabei ins Gewicht, daß der Nitrosamingehalt im Nebenstrom nach Brunnemann et al. [1, 2] bis zu 50mal höher ist als im Hauptstrom, den nur der Raucher selbst einatmet. Durch diese besonders stark erhöhte Nitrosaminmenge im Nebenstrom wird der Verdünnungseffekt so stark relativiert, daß – nach den gleichen Autoren – die Nitrosaminaufnahme von Passivrauchern in stark verqualmten Räumen Werte erreichen kann, die dem Gehalt im Hauptstrom von bis zu 30 Zigaretten stündlich entsprechen! Der Nitrosamingehalt im Nebenstrom des Tabakrauches ist zum Beispiel mindestens tausendfach höher als im Bier oder als im Aminophenazon, einem ansonsten bewährten Medikament, das wegen winziger Nitrosaminspuren aus dem Verkehr gezogen wurde, oder auch als die Höchstwerte, die kürzlich in der Nitrosaminverordnung für Babyschnuller festgelegt wurden.

Eine unschädliche Dosis gibt es nicht

4. Kanzerogene unterscheiden sich von anderen Giften durch ihre ausgeprägte Summationswirkung. Die einzelnen Teildosen addieren sich bis zu einem kritischen Schwellenwert, dessen Überschreitung in der Regel zur klinischen Manifestation des Krebses führt. Schon winzige Dosen – 1 millionstel Gramm reicht dazu schon aus – hinterlassen demnach eine irreversible Veränderung in der Zelle (= Tumorkeimanlage). Eine völlig unschädliche Dosis gibt es deshalb für krebserzeugende Stoffe grundsätzlich überhaupt nicht, weil die Möglichkeit nicht ausgeschlossen werden kann, daß die durch Passivrauchen aufgenommenen Partialdosen durch Summation mit anderen Kanzerogenen in unserer Umwelt, denen sich keiner von uns ganz entziehen kann, dazu führen, daß der krebserzeugende Schwellenwert, der sonst zu Lebzeiten des Patienten vielleicht nicht erreicht worden wäre, durch Vorverlagerung überschritten und somit der Krebs zu Lebzeiten klinisch manifest wird. Aus ebendiesem Grunde gibt es für krebserzeugende Stoffe auch keine MAK-Werte.

5. Legt man diese Gegebenheiten zugrunde, erscheinen die vorliegenden epidemiologischen Untersuchungen keineswegs unerwartet. Besonders ist in diesem Zusammenhang die Studie von Hirayama [4] an mehr als 91000 nichtrauchenden japanischen Ehefrauen im Alter von mehr als 40 Jahren zu nennen. Nichtraucherinnen zeigten danach eine mehr als doppelt so hohe Lungenkrebsrate, wenn sie mit einem Raucher, statt mit einem Nichtraucher verheiratet waren. Darüber hinaus fand er eine statistisch signifikante Relation des Lungenkrebsrisikos der Nichtraucherinnen zur Intensität des Rauchens des Ehegatten, nicht aber für andere Krebsformen (Magen- und Gebärmutterkrebs).

Gleichsinnige Befunde erhoben auch Trichopoulos et al. [14] in Athen mit einem völlig anderen methodischen Vorgehen: Beim Vergleich der Rauchgewohnheiten der Ehegatten von 51 Patientinnen mit Lungenkrebs mit denen von 163 Frauen mit anderen Krankheiten stieg die Lungenkrebsrate mit einem Raucher verheirateter Nichtraucherinnen im Durchschnitt auf das 2,4fache und – wenn der Ehemann mehr als zwei Päckchen Zigaretten täglich rauchte – sogar auf das 3,4fache.

Zumindest eine gleiche Tendenz – auch wenn sie sich nicht statistisch sichern ließ – fand Garfinkel [3] bei der nachträglichen Auswertung der Unterlagen der Prospektivstudie der American Cancer Society nach dem Muster der Studie von Hirayama [4]: Setzt man die altersberichtigte Lungenkrebsrate nichtrauchender Ehefrauen von Nichtrauchern mit 1 an, stieg sie auf 1,37, wenn die Nichtraucherinnen mit einem Raucher verheiratet waren, der mehr als 20 Zigaretten täglich rauchte.

Diese trendmäßig ähnlichen Befunde von Garfinkel wie in der Untersuchung von Hirayama könnten bei Berücksichtigung folgender Gegebenhei-

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lichen Arbeitskreis Rauchen und Gesundheit am 27. 1. 1982 mit, daß er unsere Forderungen grundsätzlich – und nicht nur in diesem speziellen Fall – für berechtigt hält und sie bei seinen weiteren Diskussionen mit Prof. Schmähl berücksichtigen wird. Beschämend ist auch, daß führende Vorstandsmitglieder der Deutschen Gesellschaft für Arbeitsmedizin, zum Beispiel G. Lehnert und H. Valentin, sich als starke Raucher nicht scheuen, alle Prinzipien der Präventivmedizin auf den Kopf zu stellen, und das Passivrauchen nur als Belästigung gelten lassen wollen, solange keine in jeder Hinsicht hieb- und stichfeste Beweise für die Gesundheitsschädlichkeit vorliegen. Nach präventivmedizinischen Grundsätzen hat jede Noxe, für deren Gesundheitsschädlichkeit ein so erdrückendes Beweismaterial vorgelegt werden kann wie für Tabakrauch prinzipiell, auch bei Verdünnung von vornherein so lange als gesundheitsschädlich zu gelten, bis umgekehrt der Nachweis vorgelegt wird, daß Passivrauchen unschädlich ist.

Summary: Passive smoking as a causal factor of bronchial carcinoma in female non-smokers

In a study on 792 patients with bronchogenic carcinoma of both sexes in the region Mannheim–Ludwigshafen–Heidelberg 59 female bronchogenic carcinomas were found. 39 of them appeared in non–smoking female patients. 61,5% of them had lived in domestic community with smokers. This is nearly the threefold as could be expected on the basis of smoking behavior of men in the respective groups of age. Suggestions on professional exposition to cancerogenic substances could not be found just as little as references to hereditary factors. Passive smoking is by far the obvious interpretation for the high share of non-smokers in our female patients with bronchogenic carcinoma the more so since the percentage of squamous cell and small-cell carcinomas which are valid as typical carcinomas of smokers, did not lie essentially lower in our non-smoking wives (66,6%) in comparison to female smokers (80%). As a further support of this interpretation is refered to similar results in the world literature proving our findings as not surprising.

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Für die Verfasser: Prof. Dr. F. Schmidt, Forschungsstelle für präventive Onkologie, Klinische Fakultät Mannheim der Universität Heidelberg, Maybachstraße 14–16, D-6800 Mannheim 1.

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The risk ratios for passive smoking can be surprisingly high (up to 2 or 3), as reported both by Correa et al and others.[8,9] These risk ratios would be more consistent with those found for active smoking, particularly among women, if the active smoker is at greater risk also from his or her own passive smoke, again through the absorption of radioactivity on the smoke particles passively inhaled; also the relatively higher toxicity of the sidestream smoke[10] might be important.[11] These and other aspects (eg, the urban-rural difference in lung cancer risk from smoking) are more thoroughly discussed elsewhere[12] in the context of indoor radon daughters. Finally, in view of the long latency periods observed among miners acquiring lung cancer from radon daughter exposure,[13] one might suggest that the children of smoking mothers obtain an early exposure to increased levels of radon daughters at home and that smoking later in life promotes the development of lung cancer.

Department of Occupational Medicine,
University Hospital,
S-581 85 Linkoping, Sweden

HANS BERGMAN
OLAV AXELSON

LUNG CANCER AND PASSIVE SMOKING

SIR,—I was surprised to read, in Professor Trichopoulos and colleagues' letter (Sept 17, p 677), a German study of passive smoking and lung cancer described as having yielded "positive" results. The paper cited[1] contains only tentative conclusions based on poor data analysed by unacceptable methods.

I was also surprised that the findings from the Greek hospital study of passive smoking and lung cancer were almost identical to those reported two years ago[2] despite a substantial increase in the numbers of cases and controls. In the 1981 report the relative risks of lung cancer for non-smoking women were 1, 1·8, 2·4, and 3·4 according to whether their husbands did not smoke, were ex-smokers, or were current smokers of 1–20 or 21 or more cigarettes a day; the updated relative risks are 1, 1·9, 2·4, and 3·4, respectively.

In the 1981 paper the relative risks agreed exactly with the appropriate cross-product ratios calculated from the numbers of cases and controls in the relevant category for husbands' smoking. In the latest results, despite the method being apparently identical, there is a clear disagreement between the relative risks provided by Trichopoulos et al and those I calculate (see table).

RELATIVE RISK OF LUNG CANCER ACCORDING TO SMOKING HABITS OF HUSBAND

Group	Non-smokers	Ex-smokers	Cigarettes per day (current smokers)	
			1–20	21+
RR (quoted)	1·0	1·9	2·4	3·4
RR (calculated)	1·0	1·9	1·9	2·5

Relative risk = ratio of risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are non-smokers.

My calculations suggest that the latest data do not show as clear an association between a woman's lung cancer risk with her husband's smoking habits as the earlier data did. Indeed, relative risks calculated from the additional data are 1, 2·0, 1·8, and 1·8 and do not show the dose-response relation seen earlier. This doubt, added to doubts about the histological evidence and the use of cases and controls from different hospitals (limitations which Trichopoulos et al concede), prompts one to ask if the study really does add to the evidence implicating passive smoking as a factor in lung cancer.

Institute of Statistics,
University of Karlsruhe,
D-7500 Karlsruhe 1, West Germany

WOLF-DIETER HELLER

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POTASSIUM CHLORIDE SUPPLEMENTS

SIR,—As your Round the World correspondent predicted,[1] the US Food and Drug Administration advisory committee meeting of March 2 on the controversy of wax-matrix versus microencapsulated potassium chloride preparations proved inconclusive. A few points about this controversy are worth noting.

The study by McMahon et al,[2] showing a favourable result for 'Micro-K' (A. H. Robins) in comparison with 'Slow-K' (Ciba-Geigy) was sponsored by Robins. The study by Patterson et al,[3] showing no difference between micro-K and slow-K, was sponsored by Ciba-Geigy. Both studies have been confirmed by other studies sponsored by the respective company.

Ciba-Geigy, while denying that slow-K is more ulcerogenic than micro-K, has bought from Alfred Benzon Ltd, Denmark, a licence for 'Kalinorm', a microencapsulated (pellet) preparation of KCl similar (or identical) to micro-K. It seems remarkable that Ciba-Geigy is planning to market this preparation when, according to Ciba-Geigy's US subsidiary, "Slow-K has an established clinical record unparalleled by any other solid K supplement".

It seems that, privately, Ciba-Geigy has concluded that kalinorm is as good as micro-K, and that it is better than slow-K, but they would presumably consider it scientifically incorrect to conclude that micro-K is better than slow-K.

Finally I would emphasise, as your RTW correspondent did, that doctors should "re-evaluate the decisive need for a potassium supplement and, if the indication is clear, prescribe it as a liquid". The findings of Patterson et al[3] clearly support this.

Furulidén 27,
S-433 64 Partille, Sweden

OLLE HANSSON

, This letter has been shown to Dr Burley, whose reply follows.—ED. L.

SIR,—One of the main reasons why slow-release formulations of potassium were developed was the unacceptability of liquid potassium. Indeed, Patterson et al[3] reported that KCP elixir was poorly tolerated in their trial, giving rise to abdominal pain and heartburn in 9 of the 15 volunteers (60%). Dr Hansson omits to mention this. The issue is therefore whether the risk/benefit ratio of 'Slow K' is acceptable. There are eighteen years of clinical experience with slow K in the UK, during which over 4·5 million patient-years of treatment has been prescribed; with 'Micro K' formulations there is almost no clinical experience. Less than 50 cases of significant alimentary side-effects have been reported with slow K, and some of these were manifestly brought about by previous strictures or oesophageal obstruction due to cardiac enlargement. It would be hard to point to a comparable safety record with any other widely used drug. The fact that a company may be investigating or pursuing alternatives is an indication of interest and involvement in the area, and should not be interpreted as a loss of confidence in an existing product.

Ciba-Geigy Pharmaceuticals,
Horsham, West Sussex

DENIS BURLEY

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PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK[1]

DALE P. SANDLER, RICHARD B. EVERSON AND ALLEN J. WILCOX

Sandler, D. P. (National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709), R. B. Everson and A. J. Wilcox. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985;121:37-48.

Overall cancer risk from adult passive smoking has been examined using smoking by spouse as the measure of exposure. Information on smoking by spouse was obtained for 518 cancer cases and 518 noncancer controls. Cancer cases were identified from a hospital-based tumor registry in North Carolina. Cases included all sites except basal cell cancer of the skin and were between the ages of 15 and 59 years at the time of diagnosis. Cancer risk among individuals ever married to smokers was 1.6 times that among those never married to smokers ($p < 0.01$). This increased risk was not explained by confounding by individual smoking habits, demographic characteristics, or social class. Elevated risks were seen for several specific cancer sites and were not limited to lung cancer or other "smoking-related" tumors. Risks from passive smoking appeared greater among groups generally at lower cancer risk (females, nonsmokers, and individuals younger than age 50 years), but were not limited to these groups.

neoplasms; risk; smoking; tobacco smoke pollution

Passive exposure to cigarette smoke has been linked with a variety of health consequences in humans, including bronchitis and pneumonia in infants (1), reduced pulmonary function (2) and acute respiratory disease in children (3–5), and decreased airway function in otherwise healthy adults (6). Several reports have also focused attention on a possible association between passive exposure to cigarette smoke and lung cancer (7–10).

In a case-control study by Trichopoulos and colleagues (7), 51 white females with lung cancer and 163 controls from an orthopedic service were compared with regard to smoking histories of husbands. Women who were not smokers but were married to smokers were at two- to threefold risk for lung cancer compared with nonsmoking women who were not married to smokers. An updated report of this study involving 77 nonsmoking lung cancer cases and 225 nonsmoking controls confirmed the twofold risk among passive smokers (8). In a prospective study from Japan, Hirayama (9) observed 245 lung cancer deaths among 91,000 married women. The lung cancer death rate for nonsmoking women married to smokers was nearly twice that for nonsmoking women married to nonsmokers and was one-half that for women who themselves smoked. Emphysema was the only other cause of death to exhibit such a pattern, although the trend was not statis-

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[1] From the Epidemiology Branch, Biometry and Risk Assessment Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Reprint requests to Dr. Dale P. Sandler, Epidemiology Branch, Mail Drop A3-02, National Institute of Environmental Health Sciences, P. O. Box 12233, Research Triangle Park, NC 27709.

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tically significant. Most recently, Correa et al. (10) reported a twofold risk for lung cancer among nonsmokers married to smokers. In contrast, analysis of data from an American Cancer Society study in the United States failed to demonstrate an association between passive exposure to cigarette smoke and lung cancer risk (11).

Many of the constituents of mainstream cigarette smoke which is actively inhaled by the smoker are present in reduced quantity in exhaled smoke (12) which is then passively inhaled by the nonsmoker. These same constituents are also contained in sidestream smoke which is released from the cigarette between active puffs and is also inhaled by the passive smoker. One might expect to find, as did Hirayama (9) for lung cancer, that for smoking-related sites, the cancer risk in individuals passively exposed to cigarette smoke might fall between that for smokers and that for nonsmokers. Risk from passive smoking might also be expected to be much lower than that from direct smoking.

However, some chemicals appear in higher concentration in sidestream smoke than in mainstream smoke, making the exposure from passive smoking qualitatively different (12, 13). The health consequences from passive smoking may, therefore, differ from those of direct smoking. These chemicals, many of which are known carcinogens, might lead to increased risk for cancer at sites not shown to be related to direct exposure to cigarette smoke. In comparing sidestream with mainstream smoke, Brunnemann (in refs. 12 and 13) found 52 times as much dimethylnitrosamine, 16 times as much naphthalene, 28 times as much methylnaphthalene, 3.4 times as much benzo(a)pyrene, and 5.6 times as much toluene, for example, in sidestream smoke as in mainstream smoke. While the concentrations of these chemicals are higher than in mainstream smoke, actual exposure from passive smoking is heavily influenced by the amount of smoke generated, the volume of ambient air, room ventilation, and the manner in which the cigarettes are smoked.

Differences in the route of inhalation of sidestream and mainstream smoke might also account for differences in site-specific effects. Wynder and Goodman (14), for example, have proposed that if sidestream smoke components are inhaled through the nasal passages, gaseous components but not smoke particulates would reach the lung.

As a preliminary exploration of the hypothesis that passive exposure to cigarette smoke may be carcinogenic, we examined adult passive exposure to cigarette smoke in relationship to cancers of all sites. Since active and passive smokers may differ in the mix of carcinogens to which they are exposed, it is not obvious which sites might be at highest risk of cancer among passive smokers. Since active smokers are also passively exposed, candidate sites might be drawn from those that have been linked with active smoking. However, there may be additional sites whose relationship to smoking has been obscured. In studies comparing smokers with nonsmokers, passive smokers are often included in the nonsmoking group. This would make it difficult to detect small differences in risk due to passive smoking. We report here on cancer risk from passive smoking using smoking histories of spouses as a measure of passive exposure to cigarette smoke during adulthood.

METHODS

Data reported here are from a study of childhood exposure to cigarette smoke and cancer risk in adulthood (29). Cases for study were selected from the hospital-based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between the ages of 15 and 59 years at the time of diagnosis and included all cancer sites ex-

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cept basal cell cancer of the skin. Cases were restricted to this age group to maximize the likelihood of also detecting effects from childhood exposure to cigarette smoke. Individuals older than 60 years in 1981 are not likely to have had mothers who smoked. Patients with multiple primary tumors were included only if the first primary tumor was diagnosed during the study period.

Cases were mailed a questionnaire for self-completion. This mailing was followed by a second mailing and then a telephone call if needed. In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer to serve as comparison subjects. These friends were the same race, sex, and age (±5 years) as the cases. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Beginning with the telephone numbers of the cases, the next higher or lower telephone numbers were called until individuals of the same race, sex, and age (±5 years) were found. For cases interviewed by telephone, the calls to identify controls were made at the same time of day. For cases contacted by mail, telephone controls were chosen during randomly assigned times of day.

Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (15 per cent) either refused (n = 71) to participate or could not be contacted. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

Of 518 cases, 360 (70 per cent) named friends or acquaintances who could be contacted as controls. Of these, 86 per cent were successfully contacted for an overall response rate of 60 per cent. To obtain the additional 209 controls, 1,237 households were telephoned. Screening data (age, race, sex, and cancer history of household members) were obtained for 988 households (80 per cent); 224 (23 per cent) of these households had a qualifying member. Fifteen (7 per cent) qualifying telephone controls refused to participate. The overall response rate for selection of telephone controls was 75 per cent (80 per cent × 93 per cent). Although not shown here, data were analyzed separately by control selection group, and the adjusted results were identical to those obtained when the control groups were combined.

Procedurally, the control selection process involved one-to-one matching. This was done to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are for unmatched data to maximize the study sample size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Parallel analyses for matched pairs were carried out. Although not presented here, the results were similar.

Passive exposure to cigarette smoke during adulthood was estimated from a questionnaire report of the number of years of marriage during which a spouse smoked. Subjects were considered exposed if they had a spouse who smoked regularly at any time during their marriage. Regular smoking was defined as smoking at least one cigarette per day for as long as six months. The nonexposed group consisted of persons married to nonsmokers and persons who never married. The quantity smoked was reported as the average number of cigarettes smoked per day by a spouse while married to a study subject.

For the analysis of questionnaire data, odds ratios were calculated, and the chi-square test was used to assess statistical significance. Combined estimates of the odds ratio (OR) in stratified analyses were obtained using the Mantel-Haenszel technique (15). The method of Gart (16) was used to obtain 95 per cent confidence limits

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for the combined estimates of the odds ratio. When the 95 per cent confidence limits did not include unity, the odds ratio was considered statistically significant ($p < 0.05$). Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified and adjusted analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, and 50+ years) and three levels of education (<12 years, 12 years, and >12 years).

Results

The distribution of cases by cancer site is shown in table 1. The young age of cases, the referral nature of the hospital, and the fact that the study was limited to living cases account for the distribution of cancers seen. There was a predominance of breast cancers, female genital tract cancers, and leukemia and lymphoma, and a relative lack of respiratory tumors. Eligible cases with respiratory cancer were significantly more likely to die before they could be contacted for this study.

Cases and controls are compared in table 2. Cases and controls are, by design, distributed similarly by race and sex, with 70 per cent of each group white and 67 per cent female. The mean age of cases (43.6 years) and controls (43.5 years) is also similar. Level of education differs significantly between groups; 45 per cent of cases and 36 per cent of controls never graduated from high school. Level of education, therefore, is taken into consideration in most analyses. On the other hand, cases and controls do not differ by broad occupational category. A greater proportion of controls never married (16 per cent vs. 13 per cent), but this difference is not statistically significant. Cancer cases and controls also do not differ in reported smoking histories. In part this is due to the relative absence of lung cancer cases and to the method of control selection. Sixty per cent of controls are friends of cases, and the smoking habits of individuals who are friends may be similar. When only cases with population controls are included, 57 per cent of cases and 46 per cent of population controls were smokers.

The overall crude cancer risk for individuals ever married to smokers is 1.6 times that for those not married to smokers ($p < 0.01$) (table 3). Adjusting independently

TABLE 1

Distribution of cancer cases by site of primary tumor and study status

Site	ICD* No.	Included		Refused or lost	
		No.	(%)	No.	(%)
Lip, oral cavity, and pharynx	140–149	22	(4)	15	(7)
Digestive organs and peritoneum	150–159	41	(8)	16	(7)
Respiratory and intrathoracic organs	160–165	32	(6)	43	(19)†
Bone, connective tissue, and skin	170–173	42	(8)	13	(6)
Breast	174	60	(12)	16	(7)
Female genital organs	179–184	175	(34)	61	(28)
Prostate	185	10	(2)	0	(0)
Testis	186	6	(1)	3	(1)
Urinary tract	188, 189	6	(1)	9	(4)
Eye, brain, and other nervous system	190–192	38	(7)	20	(9)
Thyroid and other endocrine glands	193, 194	27	(5)	3	(1)
Lymphatic and hematopoietic tissue	200–207	52	(10)	13	(6)
Site unspecified	199	7	(1)	10	(5)
All sites		518	(100.0)	222	(100.0)

* $p < 0.01$.

† ICD, *International Classification of Diseases*, Ninth Revision.

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TABLE 2
Comparison of cases and controls

Factor	Cases No. (%)	Controls No. (%)
Total	518 (100)	518 (100)
Age		
<30	96 (19)	99 (19)
30–39	89 (17)	105 (20)
40–49	132 (25)	121 (23)
50+	201 (39)	193 (37)
Race		
Nonwhite	153 (30)	153 (30)
White	365 (70)	365 (70)
Sex		
Male	169 (33)	169 (33)
Female	349 (67)	349 (67)
Marital status*		
Never married	65 (13)	79 (16)
Ever married	444 (87)	410 (84)
Education†		
<12 years	233 (45)	186 (36)
12 years	137 (27)	186 (36)
>12 years	147 (28)	146 (28)
Occupation‡		
Blue collar	172 (35)	194 (38)
White collar	192 (39)	175 (34)
Housewife	118 (24)	131 (26)
Unemployed	8 (2)	11 (2)
Smoking		
Never	235 (45)	247 (48)
Ever	283 (55)	271 (52)
Current	154 (30)	166 (32)
Past	129 (25)	105 (20)

* Nine cases and 29 controls did not report marital status.

† One case did not report years of education.

‡ Twenty-eight cases and seven controls did not report occupation.

and in combination for sex, age, race, smoking, parental smoking, education, and occupation does not change this finding. Cancer risk from passive exposure to cigarette smoke appears greatest for females and for individuals who are not themselves smokers, with statistically significant risks limited to these subgroups. There are no apparent subgroup differences in risk with race or occupational category (blue collar or white collar), although risk appears greater for individuals with at least a high school education. Cancer risk in relationship to passive exposure to cigarette smoke also appears limited to individuals who are younger than age 50 years.

Cancer risks from passive smoking among smokers and nonsmokers are shown separately in table 4. Risk is clearly elevated among nonsmokers, with the twofold risk significant after adjustment for age, race, or sex. Risk is also elevated among smokers, but the 30 per cent increase in risk is only of borderline statistical significance. Among nonsmokers, risk does not differ with race, but the risk from passive exposure is statistically significant only among females and among individuals between the ages of 30 and 49 years, although it is also elevated for males. For smokers, risk is significantly elevated among females and whites. The twofold risk related to passive exposure among individuals younger than 30 years (table 3) is due to risk among individuals who are themselves smokers (OR = 2.3) (table 4). The lower risk among nonsmokers in this age group (OR = 1.4) contrasts with the greater risk among nonsmokers in the other age categories under age 50 years. This suggests that the cumulative exposure through passive means, alone, for this young group may be below that which would pose a risk.

For most cancer sites, the number of cases is too small for meaningful site-specific analysis. However, statistically significant risks in relationship to passive smoking are seen for breast cancer, cervical cancer, and endocrine cancers. Odds ratios adjusted for possible differences in the distributions of age and level of education are shown in table 5 for smokers and nonsmokers combined.

The twofold risk of breast cancer shown in table 5 is not substantially changed by adjustment for education, race, age, smoking status, or parental smoking. Breast cancer risk is greater among younger women (OR = 3.4 for women <50 years vs. OR = 1.1 for women ≥50 years) and those with at least a high school education (OR = 3.3 vs. OR = 1.0).

The twofold risk for cervical cancer

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TABLE 5

Overall cancer risk from smoking by spouse, adjusted separately† for potential confounding factors

Factor	% exposed‡		Crude OR†	Adjusted OR	95% CL† on adjusted OR
	Cases§ (n = 508)	Controls (n = 489)			
Crude risk	55	43	1.6**		(1.3, 2.1)
Sex					
Male	35	26	1.5**		
Female	65	51	1.8**	1.7**	(1.3, 2.2)
Age					
<30	39	24	2.0*		
30–39	55	39	1.9*	1.6**	(1.3, 2.1)
40–49	67	47	2.2**		
50+	56	54	1.2		
Race					
Nonwhite	50	34	1.6*		
White	58	45	1.7**	1.6**	(1.3, 2.1)
Smoking					
Nonsmokers	52	34	2.1**		
Smokers	58	51	1.3	1.6**	(1.3, 2.1)
Education					
<12 years	55	52	1.1		
12 years	61	35	2.9**	1.6**	(1.2, 2.1)
>12 years	50	41	1.5		
Occupation¶					
Blue collar	53	40	1.7*		
White collar	53	40	1.7*	1.7**	(1.2, 2.3)
Either parent smoked					
No	55	41	1.8**	1.8**	(1.3, 2.3)
Yes	57	44	1.7**		

* $p < 0.05$.

** $p < 0.01$.

† OR, odds ratio, after multiple adjustment for age, race, sex, education, and smoking status = 1.7, 95% confidence limits (CL) = (1.3, 2.3).

‡ Spouse ever smoked while married to study subject.

§ Numbers of cases are not equivalent to those shown in table 1 because of missing values for education or spouse smoking.

¶ Excludes housewives, those unemployed, and those missing data on occupation.

among individuals passively exposed to cigarette smoke is also not affected by adjustment for age, race, smoking status, or smoking by parents. The estimated risk is reduced somewhat by adjustment for level of education, but there is no clear pattern of risk with level of education. As for the other sites, risk appears greatest among younger women (OR = 2.9 for women <50 years vs. OR = 0.9 for women ≥50 years). Odds ratios are statistically significant for whites and for nonsmokers, but the magnitude of the risks for nonwhites and for smokers is similar.

There is also a statistically significant risk of endocrine tumors among exposed individuals, which remains after adjustment for potential confounding variables. In subgroup analyses, risk is significant for younger individuals, nonsmokers, individuals with a high school education, and individuals whose parents did not smoke.

Although the number of lung cancer cases is small (n = 22), lung cancer risk from passive exposure to cigarette smoking is examined in table 6 because of current interest in this site. The overall crude risk of 1.9 is not statistically significant. However, the odds ratios for females (OR = ∞) and for nonsmokers (OR = ∞) are statisti-

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TABLE 4

Overall cancer risk from passive exposure to cigarette smoke among smokers and nonsmokers, adjusted for potential confounding factors

Factor	Nonsmokers (n = 466)				Smokers (n = 532)			
	Cases†	Controls	Crude OR‡	Adjusted OR‡ (95% CL§)	Cases†	Controls	Crude OR‡	Adjusted OR‡ (95% CL§)
	No. (% exposed)	No. (% exposed)			No. (% exposed)	No. (% exposed)		
Crude risk	231 (52)	235 (34)	2.1**		278 (58)	254 (51)	1.3	
				(1.4, 3.0)				(0.9, 1.9)
Age								
<30	45 (22)	58 (17)	1.4		50 (54)	38 (34)	2.3	
30–39	36 (56)	49 (31)	2.8*	2.0**	51 (55)	48 (48)	1.3	1.4
40–49	63 (68)	48 (33)	4.3**	(1.4, 2.9)	67 (64)	66 (58)	1.3	(1.0, 1.9)
50+	87 (53)	80 (49)	1.2		110 (58)	102 (55)	1.1	
Sex								
Male	39 (13)	57 (9)	1.5	2.0**	128 (41)	102 (36)	1.2	1.5*
Female	192 (59)	178 (42)	2.0**	(1.3, 2.9)	150 (73)	152 (61)	1.7*	(1.0, 2.1)
Race								
Nonwhite	72 (53)	83 (31)	2.5**	2.0**	77 (47)	63 (48)	1.0	1.4
White	159 (51)	152 (36)	1.9**	(1.4, 3.0)	201 (63)	191 (52)	1.5*	(1.0, 1.9)

* $p < 0.05$.

** $p < 0.01$.

† Numbers of cases are not equivalent to those shown in table 1 because of missing values for spouse smoking.

‡ OR, odds ratio.

§ CL, confidence limits.

cally significant even though they are based on small numbers. Since only two lung cancer cases were nonsmokers and only seven were females, it is not possible to examine lung cancer in greater detail. Risk is also elevated among younger individuals and among those with at least a high school education.

Among nonsmokers alone, risks were significantly elevated for endocrine and cervical cancer, despite the loss of power from reducing the already small number of cases for site-specific analysis (table 7). The twofold risk for breast cancer seen overall is also seen for nonsmokers but is not quite statistically significant. Among smokers, the odds ratio is statistically significant for breast cancer only. However, the approximately twofold risk for cervical cancer is similar to that among nonsmokers.

There is no clear dose-response relationship for all cancer sites combined or for specific sites in relationship to either the number of years married to a smoker (adjusted for age) or the average number of cigarettes smoked per day. This is true for smokers and for nonsmokers and also when analysis is confined to those younger than age 50 years, to whom an effect of passive smoking appears limited.

DISCUSSION

We have found a significantly elevated overall cancer risk for individuals passively exposed to cigarette smoke. This cannot be readily explained by a number of other factors, including individual smoking habits and two measures of social class: education and broad occupational category. Elevated risks were seen for several specific cancer sites and were not limited to lung cancer or other "smoking-related" tumors. These findings might relate to other factors we have not measured or to deficiencies in study design. However, we have not been able to identify a possible confounder or a bias of selection or recall that could have caused the difference in smoking patterns of spouses between cases and controls. Study subjects and interviewers were told

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TABLE 5

Cancer risk from passive exposure to cigarette smoke, adjusted for age and education, all sites combined and specific sites

Site	Cases	Crude OR§	Adjusted OR§	95% CL‖ on adjusted OR§
	No.† (% exposed)‡			
All sites	508 (55)	1.6**	1.6**	(1.2, 2.1)
Lip, oral cavity, and pharynx	22 (55)	1.6	1.1	(0.4, 3.0)
Digestive system	39 (51)	1.4	1.0	(0.5, 2.2)
Respiratory system	32 (50)	1.3	1.0	(0.5, 2.4)
Lung	22 (59)	1.9	1.5	(0.6, 4.3)
Bone, connective tissue, and skin	42 (36)	0.7	0.7	(0.3, 1.5)
Breast¶	59 (69)	2.2**	1.8*	(1.0, 3.7)
Female genital system¶	170 (66)	1.9**	1.8**	(1.2, 2.8)
Cervix	101(67)	2.0**	1.8*	(1.1, 3.2)
Prostate¶	10 (30)	1.2	0.8	(0.1, 3.9)
Testis¶	5 (40)	1.9	2.6	(0.2, 49.9)
Urinary tract	6 (50)	1.3	1.1	(0.2, 7.6)
Eye, brain, and other nervous system	38 (32)	0.6	0.7	(0.3, 1.5)
Endocrine	26 (65)	2.5*	3.2**	(1.4, 9.4)
Hematopoietic	52 (44)	1.1	1.3	(0.7, 2.5)
Other	7 (57)	1.8	1.8	(0.3, 10.4)

* $p < 0.05$.

** $p < 0.01$.

† Numbers of cases are not equivalent to those shown in table 1 because of missing values for education or spouse smoking.

‡ For comparison, 210 of 489 controls (43%) were exposed.

§ OR, odds ratio.

‖ CL, confidence limits.

¶ Sex-specific comparison. Of 330 female controls, 51% were exposed. Of 159 male controls, 26% were exposed.

simply that the study was designed to look at smoking patterns in families.

Cases and controls were similar with regard to their own smoking histories. This was partly because of the choice of friend controls who tended to have similar smoking histories and because known smoking-related sites were underrepresented in the case population. Cases included in the study were generally younger than those with smoking-related tumors. Unavoidable delays between case identification and completion of interviews also contributed to the lack of smoking-related cancers. Persons with lung cancer and other smoking-related tumors were more likely to have died before they could be interviewed. In addition, because of the special interests of physicians at the hospital from which cases were identified, breast cancers and gynecologic cancers were overrepresented. As a result of this unintentional matching on smoking status, risks from passive smoking and direct smoking cannot be compared.

The route of exposure for the passive smoker is via inhalation. Reports of effects on upper respiratory tract function (2–6) are consistent with this. There has also been a report of mutagens measured in the urine of passive smokers (17), indicating that components of cigarette smoke enter the bloodstream and are circulated throughout the body of the passive smoker. Another report indicated that enzyme activity can be induced by passive exposure to cigarette smoke (18). These findings are tentative, but do suggest that an overall increase in cancer risk or an increase in risk for specific nonrespiratory sites following passive exposure to cigarette smoke is plausible.

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TABLE 6

Lung cancer risk from passive exposure to cigarette smoke, adjusted for potential confounding factors

Factor	Cases No. (% exposed)	Crude OR†	Adjusted OR†	95% CL‡ on adjusted OR†
Crude risk	22 (59)	1.9		(0.8, 5.0)
Sex				
Male	15 (40)	1.9		(1.1, 8.4)
Female	7 (100)	∞**	3.4*	
Smoking				
Nonsmokers	2 (100)	∞*		
Smokers	20 (55)	1.2	1.5	(0.6, 3.9)
Age				
<50	5 (80)	6.7		
50+	17 (53)	1.0	1.5	(0.6, 3.8)
Education				
<12 years	15 (47)	0.8		
12 years	4 (100)	∞**	1.6	(0.6, 4.4)
>12 years	3 (67)	2.8		
Either parent smoked§				
No	6 (50)	1.5	1.5	(0.5, 4.8)
Yes	9 (56)	1.6		

* $p < 0.05$.
** $p < 0.01$.
† OR, odds ratio.
‡ CL, confidence limits.
§ Numbers reduced because of missing data on parental smoking.

TABLE 7

Cancer risk from passive exposure to cigarette smoke among smokers and nonsmokers: selected sites

Site	Nonsmokers			Smokers		
	No. of cases	Odds ratio	(95% CL†)	No. of cases	Odds ratio	(95% CL†)
Lung	2	∞‡		20	1.2	(0.5, 2.9)
Breast	32	2.0	(0.9, 4.3)	27	2.8*	(1.0, 7.6)
Cervix	56	2.1*	(1.2, 3.9)	45	2.0	(0.9, 4.1)
Endocrine glands	13	4.4*	(1.2, 17.4)	13	1.5	(0.4, 5.5)

* $p < 0.05$.
† CL, confidence limits.
‡ $p = 0.051$.

Our study was intended to consider a range of effects similar to what might be measured in a prospective study of a cohort of individuals who are passively exposed. Such an approach serves to single out sites which appear to be important as well as to investigate whether passive exposure might increase susceptibility to additional insults, thereby increasing cancer risk overall. Two reports in the literature use prospectively collected data (9, 11). One of these (11), however, does not provide data on cancer risks at sites other than the lung, and neither report provides data on overall cancer risk from passive exposure to cigarette smoke. Data from the Japanese study recently presented by Hirayama, however, indicate that cancer risk may be increased at sites other than the lung and that risk may not be limited to smoking-related sites (Hirayama, personal communication: presented at Hawaii Cancer Conference, 1984).

For this study, passive exposure during adult life is determined from a question-

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naire report of the number of years of married life during which a spouse smoked. Misclassification of exposure status is likely for individuals who never married but have lived with other persons who smoked. Slightly more controls than cases reported never marrying, which might lead to differential misclassification. However, we reanalyzed our data, excluding subjects who never married, and found the results to be the same. When only married subjects were included, the odds ratio for cancers of all sites combined was also 1.6. We made no allowances for multiple spouses, other members of the household who smoke, or passive exposures which occur outside of the home. Quantity smoked, too, is an approximate measure. The reported number of cigarettes smoked per day by the spouse is simply the average daily amount smoked during that time period. No allowance was made for changes in smoking habits of the spouse over time or for time since last exposure if the spouse did not smoke during the entire married interval.

Nonetheless, we found smoking by spouse to be significantly associated with overall cancer risk. The odds ratio of 1.6 was not substantially altered by adjustment for age, race, sex, smoking status, education, or occupation. Risk was limited to individuals younger than age 50 years, who were at approximately twofold risk. Risk was also greatest for females and nonsmokers, although not entirely limited to these groups.

When smokers and nonsmokers are considered separately, the twofold risk among nonsmokers is highly significant and is not altered by adjustment for potential confounding factors. The 30 per cent increase in risk among smokers whose spouses also smoke is only of borderline statistical significance, but is also unchanged by adjustment for other factors. The groups for whom risk from passive smoking appeared greatest are those groups generally at lower cancer risk overall. It may be that the small risk imposed by passive exposure during adult life is difficult to detect statistically in individuals at risk from other causes. Also, women who smoke may tend to smoke less, start later, and inhale differently than men. This would allow for a greater impact of passive exposure among women, regardless of their own smoking status. In addition, very few nonsmoking men are married to smokers, making it more difficult to detect a risk among males. In our data, only 10 per cent (10/96) of nonsmoking males were married to smokers, whereas 51 per cent (189/370) of nonsmoking females were married to smokers.

The increased cancer risk from passive exposure was not limited to sites generally thought to be smoking-related (12, 13). In fact, because of our case selection procedures and delays in interviewing cancer cases, individuals with cancers of smoking-related sites were only a small proportion of total cases. If cancers of the esophagus, respiratory tract, oral cavity and pharynx, urinary tract, and pancreas are designated smoking-related, the odds ratio for smoking-related tumors is 1.3, whereas the odds ratio for other sites is 1.7 ($p < 0.01$). Evidence is accumulating that cancer of the cervix should also be included among those sites that are smoking-related (19–21). When the cervix is included, the odds ratio for smoking-related sites is 2.0 and for other sites is 1.5, both of which are statistically significant.

Only 22 lung cancer cases are included in this report, with an odds ratio of 1.9 among passive smokers. Although not statistically significant, it is consistent with the level of risk reported in other studies. For women and for nonsmokers, the risk of lung cancer among those passively exposed was significantly increased despite very small numbers. The odds ratio for individuals under age 50 years was of borderline significance. Hirayama (9) reported a twofold risk for women married to smokers and found that risks were also greatest among younger women (as measured by husband's age). While Garfinkel (11) didn't find an

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overall relationship of passive exposure to lung cancer risk, the relative risk among women married to smokers was in the same direction. Relatively few women in Garfinkel's cohort were under age 50 years, which might explain these inconsistent results.

In a study reported by Correa et al. (10), a twofold relative risk was seen among nonsmokers married to smokers. The risks were similar for males and females, although the number of nonsmoking males with lung cancer was very small. Among smokers, males who were light smokers with wives who were heavy smokers had a relative risk of 1.5. Trichopoulos et al. (7, 8) also reported an overall twofold lung cancer risk which was statistically significant among nonsmoking women married to smokers.

The studies reported by Trichopoulos et al. (7, 8), Correa et al. (10), and Hirayama (9) all suggest a dose-response relationship, although different measures of dose were employed in the three studies. In our study, there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose, but the number of lung cancer cases may be too small to expect a consistent trend. Evaluation of dose is not straightforward and depends on factors which we did not measure, such as room ventilation and smoking "style" of the spouse.

We found a twofold cervical cancer risk, which persisted after adjustment for level of education, among women whose husbands smoked. We did not collect data on sexual activity of cases or spouses. We also see an increased risk of breast cancer. Since the sociodemographic risk factors for these two sites are not the same, this supports the conclusion that the apparent excess cervical cancer risk is not entirely due to confounding by social class. Buckley et al. (22) reported a fourfold risk of cervical cancer among women whose husbands smoked, but after adjustment for number of sexual partners of the husband, the resulting twofold relative risk was not significant. Similar results were reported by Brown et al. (23). Hirayama (9) did not find elevated cervical cancer risk among women whose husbands smoked. This may relate to differences in the ages of the women studied or to differences in risk from other factors.

No previous study has reported a positive association between breast cancer and either passive or direct exposure to cigarette smoke (24–26). In a recently reported study by Rosenberg et al. (27), the relative risk for breast cancer was approximately 1.0 for exsmokers, current smokers, and heavy smokers as compared with nonsmokers. The crude odds ratio of 2.2 that we report is not reduced by adjustment for a number of potential confounding variables. Risk is not seen among women older than age 50 years or among women with less than a high school education, but is fairly constant across all other groups. Petrakis (28) has detected nicotine in breast fluid of nonlactating women who smoked, which may lead to alterations in breast tissue. This would support a possible role for passive smoking if passive exposure also caused such an effect.

One other site for which we find an association with passive exposure, endocrine glands, is not generally thought to be smoking-related. The number of tumors here is small, of which 11 are thyroid tumors.

In summary, passive exposure to smoking by spouse is related to an overall risk of cancer in our data. This association persists after adjusting for possible confounding factors. Associations with several specific tumor sites are also statistically significant, including some which are not ordinarily regarded as smoking-related. Further studies are required to confirm this broad spectrum of carcinogenicity by passive smoking and to explore the unexpected site-specific findings.

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Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking

DALE P. SANDLER, MPH, PHD, RICHARD B. EVERSON, MD, ALLEN J. WILCOX, MD, PHD, AND JAMES P. BROWDER, MD

Abstract: We obtained data on smoking by parents from 438 cancer cases and 470 controls to investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke. Cancer cases were between ages 15 and 59 at time of diagnosis. All sites but basal cell cancer of the skin were included. Cancer risk was increased 50 per cent among offspring of men who smoked. Increased risk associated with father's smoking was not explained by demographic factors, social class, or individual smoking habits, and was not limited to known smoking related sites.

Relative risk (RR) estimates associated with father's smoking tended to be greatest for smokers, males, and non-Whites. There was only a slight increase in overall cancer risk associated with maternal smoking. Mother's and father's smoking were both associated with risk for hematopoietic cancers, and a dose-response relationship was seen. The RR for hematopoietic cancers increased from 1.7 when one parent smoked to 4.6 when both parents smoked. Although they should be considered tentative, study findings suggest a long-term hazard from transplacental or childhood passive exposure to cigarette smoke. (*Am J Public Health* 1985; 75:487–492.)

Introduction

Cancer risk in adult life may be affected by transplacental and childhood exposure to cigarette smoke.[1] Data from studies in animals have demonstrated that many carcinogens are active when administered transplacentally or during early life. In some instances, effects may be produced at lower doses than are required for adults.[2–6] The tumors resulting from these transplacental and early postnatal exposures may not be apparent until adulthood.[3,7–9]

Studies in humans demonstrate that the fetus of smoking parents is exposed to components of cigarette smoke and is capable of bioactivating these chemicals.[10–20] For example, cotinine has been measured in the amniotic fluid of smokers and passive smokers[13] and thiocyanate has been measured in fetal cord blood.[14–16] Studies have also demonstrated increased activity of enzymes that metabolize benzo(a)pyrene in placentas of women who smoke,[17–19] and possibly even in placentas of women passively exposed to cigarette smoke.[20] Similar elevations may occur in the tissues of the fetus or exposed child. Finally, increased urinary excretion of mutagens has been found in passive smokers.[21]

Several epidemiologic studies have demonstrated increased risk for childhood tumors in relation to either paternal or maternal smoking,[22–24] but not all studies demonstrate an increased risk.[25,26] Even if no increased risk of childhood cancer were found, however, it would not rule out the possibility of increased cancer risk during adult life from fetal or childhood exposure. One recent study found elevated lung cancer risk for individuals whose mothers smoked.[27]

Cigarette smoke contains many known carcinogens.[28] Sidestream smoke, which is the smoke released from the cigarette between active puffs, may differ qualitatively from the mainstream smoke which is inhaled by the active smoker.[29] Some compounds occur in markedly higher concentrations in sidestream smoke, and although this smoke is diluted by the ambient air into which it is released, the passive smoker may inhale smoke which is qualitatively richer in certain compounds than mainstream smoke (Hoffman in 28). For example, the concentration of dimethylnitrosamine in sidestream smoke is 52 times that in mainstream smoke. Such qualitative differences make it difficult to predict the biologic effect of exposure to sidestream smoke.

In this study we investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke.

Methods

Our study methods have been described in greater detail elsewhere.[29] Cancer cases were selected from the hospital based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between ages 15 and 59 at time of diagnosis and included all cancer sites except basal cell cancer of the skin. Cases were restricted to age 59 and younger, since fewer than 5 per cent of women of child bearing age in 1920 were smokers.[30,31]

Cases were mailed a questionnaire for self completion, followed by a second mailing and a telephone call if needed. Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (16 per cent) either refused (n = 71) to participate or could not be contacted. Cases who died or did not respond were slightly older and were more often male or non-White; cases with respiratory cancer were more likely to have been excluded, presumably due to higher case fatality. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer and were the same race, sex, and age (± 5 years) to serve as comparison subjects. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Data were analyzed separately by control selection group and the adjusted results were nearly identical to those obtained when the control groups were combined.

Address reprint requests to Dale P. Sandler, MPH, PhD, Epidemiology Branch, Biometry and Risk Assessment Program, National Institute of Environmental Health Sciences, Mail Drop A3-02, P.O. Box 12233, Research Triangle Park, NC 27709. Drs. Everson and Wilcox are also with NIEHS. Dr. Browder is with the Department of Surgery, School of Medicine, University of North Carolina, Chapel Hill. This paper, submitted to the Journal May 1, 1984, was revised and accepted for publication October 16, 1984.

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Individuals were specifically requested to supply information on natural parents. Only individuals who lived with both natural parents for all or most of the first 10 years of life are included in this report. As a result, 128 individuals were excluded (80 cases and 48 controls).

Transplacental and childhood exposure to cigarette smoke was assessed from questionnaire reports of smoking histories of parents. Subjects were asked whether parents ever smoked, smoked before the subject's birth, smoked in the house for most of the years before the subject was 10 years old, and whether mothers smoked while pregnant with the study subject. Subjects were also asked the usual quantity of cigarettes smoked by the parents and the frequency of smoking in the house. For this report, unless otherwise specified, exposure is classified by parental smoking in the household before the subject attained 10 years of age.

For this report, "smoking related" tumors were defined as cancer of the oral cavity and pharynx, esophagus, pancreas, respiratory and intrathoracic organs, urinary tract and cervix.[25] Because evidence linking cervical cancer with cigarette smoking is not well documented, we also analyzed these data with cervical cancer excluded from this designation. The number of "smoking related" tumors was substantially reduced by this exclusion, but the general findings were not altered. For individual smoking status, smokers are defined to include anyone who ever smoked at least one cigarette a day for as long as six months. Nonsmokers are individuals who have never smoked.

Estimates of the relative risk (RR) in stratified analyses were obtained using the Mantel-Haenszel technique[32] for the summary odds ratio. The method of Gart[33] was used to obtain 95 per cent confidence limits for the combined estimates of RR. Estimates of the relative risk adjusted simultaneously for multiple confounding variables were obtained using a multiple logistic model.

Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, 50+) and three levels of education (<12 years, 12 years, >12 years). Age was treated as a continuous variable in the multiple logistic analysis.

Controls were matched one-to-one to cases to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are unmatched to maximize the study size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Analyses using matched pairs gave similar results.

Results

Cases and controls are distributed similarly by age, race, and sex (Table 1). Cases and controls differ only in their distribution by years of schooling with fewer cases having completed high school. However, cases and controls are similar in broad occupational categories. Cases and controls are similar with regard to their own smoking status with 45 per cent of cases and 47 per cent of controls never having smoked; the similarity is largely due to the use of friends as controls. When only cases with population controls are included, 57 per cent of cases and 47 per cent of population controls were smokers.

Maternal Smoking

There was only a small difference between cases and controls in reported exposure to maternal smoking [estimated relative risk (RR) = 1.1, 95 per cent confidence limits = 0.7, 1.6]. The RR for cancer among individuals whose mothers smoked was close to one for all measures of maternal smoking, and this lack of association persisted after adjustment for potential confounding factors including age, race, sex, education, individual smoking, and method of control selection.

Site specific relative risk estimates were calculated for 13 different sites, even though for many sites the number of cases is too small for detailed analysis. For most sites, the RR in relation to maternal smoking was close to one (Table 2). However, the RR for leukemia and lymphoma was 2.7 (95 per cent confidence limits = 1.3, 5.8). The RR for hematopoietic cancers associated with maternal smoking is greater for individuals whose fathers also smoked (2.6 vs 1.5 for nonsmoking fathers), but the RR remained elevated (RR = 2.4, 95 per cent confidence limits = 1.0, 5.5) after adjusting for father's smoking. Adjustment for age, race, sex, education, and individual smoking did not change this finding. The numbers of specific hematopoietic cancers are small precluding detailed analysis. However, the crude RR for Hodgkins disease (RR = 4.4, 95 per cent confidence limits = 1.1, 4.6), non-Hodgkins lymphomas (RR = 1.7, 95 per cent confidence limits = 0.5, 5.2) and acute leukemias (RR = 8.8, 95 per cent confidence limits = 2.0, 40.0) were greater than one.

TABLE 1—Comparisons of Cases and Controls

Factor	Cases N (%)	Controls N (%)
Total	438 (100)	470 (100)
Age (years)		
<30	83 (19)	89 (19)
30–39	72 (16)	95 (20)
40–49	117 (27)	110 (23)
50–59	166 (38)	176 (37)
Mean Age	43	43
Race		
White	325 (74)	340 (72)
Non-White	113 (26)	130 (28)
Sex		
Male	147 (34)	158 (34)
Female	291 (66)	312 (66)
Education†		
<12 years	182 (42)	164 (35)
12 years	122 (28)	171 (36)
>12 years	133 (30)	135 (29)
Occupation†		
Blue Collar	158 (39)	154 (34)
White Collar	154 (38)	183 (40)
"Housewife"	97 (24)	118 (26)
Smoking Status		
Nonsmoker	197 (45)	223 (47)
Smoker	241 (55)	247 (53)
Mother's Smoking†		
No	353 (84)	389 (85)
Yes	65 (16)	66 (15)
Father's Smoking†		
No	166 (44)	234 (53)
Yes	212 (56)	204 (47)

†Numbers reduced because of missing values.

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TABLE 2—Cancer Risk from Mother's Smoking, All Sites Combined and Selected Sites

Site	Cases		Crude RR	95% Conf. limits
	No.	(% exposed)†		
All Sites	418*	(16)	1.1	(0.7, 1.6)
"Smoking Related"	131	(13)	0.9	(0.5, 1.6)
Not "Smoking Related"	287	(17)	1.2	(0.8, 1.8)
Lip, Oral Cavity and Pharynx	17	(12)	0.8	(0.2, 3.5)
Digestive System	31	(10)	0.6	(0.2, 2.1)
Respiratory System	22	(14)	0.9	(0.3, 3.2)
Lung	15	(13)	0.9	(0.2, 4.1)
Bone, Skin and Connective Tissue	36	(8)	0.5	(0.2, 1.8)
Breast‡	53	(15)	0.9	(0.4, 2.1)
Female Genital Tract‡	133	(17)	1.1	(0.7, 2.2)
Cervix‡	80	(15)	0.9	(0.6, 1.9)
Prostate§	10	(0)	0.0	(0.0, 3.7)¶
Testis§	5	(20)	1.8	(0.2, 16.6)
Urinary Tract	6	(0)	0.0	(0.0, 5.1)¶
Eye, Brain and Other Nervous System	37	(11)	0.7	(0.2, 2.1)
Brain	31	(13)	0.9	(0.3, 2.7)
Endocrine Glands	21	(19)	1.4	(0.5, 4.2)
Hematopoietic Tissue	41	(32)	2.7	(1.3, 5.8)
Other	6	(17)	1.2	(0.1, 10.3)

*Missing values for mother's smoking
†For comparison 66 (15%) of 455 controls were exposed to mother's smoking
‡Sex specific comparison 16% of 301 female controls were exposed
§Sex specific comparison 12% of 154 male controls were exposed
¶Exact confidence limits

Paternal Smoking

There was an overall relative risk estimate of 1.5 (95 per cent confidence limits = 1.1, 2.0) for cancer among individuals whose fathers smoked in the household (Table 3). Adjusting for potential differences in age, sex, race, individual smoking status, smoking by spouse, education, maternal smoking, or method of control selection did not alter this finding (RR = 1.5). Estimates of the adjusted RR were obtained separately for the group with friend controls (RR = 1.6) and the group with population controls (RR = 1.4). The combined adjusted RR in a matched pairs analysis with a much smaller data set was also similar. The RR for cancer associated with father's smoking was greater for males than females (1.7 vs 1.4), for non-Whites than for Whites (1.7 vs 1.4), and for smokers than for nonsmokers (1.7 vs 1.2).

TABLE 3—Cancer Risk from Father's Smoking, All Sites Combined and Selected Sites

Site	Cases		Crude RR	95% Conf. limits
	No.	(% exposed)†		
All Sites	378*	(56)	1.5	(1.1, 2.0)
"Smoking Related"	120	(58)	1.6	(1.0, 2.5)
Not "Smoking Related"	258	(55)	1.4	(1.0, 1.9)
Lip, Oral Cavity and Pharynx	17	(53)	1.3	(0.4, 3.8)
Digestive System	30	(60)	1.7	(0.8, 3.9)
Respiratory System	22	(50)	1.1	(0.5, 2.9)
Lung	13	(62)	1.8	(0.5, 6.6)
Bone, Skin and Connective Tissue	34	(32)	0.5	(0.2, 1.2)
Breast‡	51	(51)	1.1	(0.6, 2.1)
Female Genital Tract‡	113	(60)	1.6	(1.0, 2.6)
Cervix‡	70	(61)	1.7	(1.0, 3.0)
Prostate§	9	(44)	1.0	(0.2, 4.7)
Testis§	5	(80)	5.2	(0.5, 125.9)
Urinary Tract	5	(40)	0.8	(0.1, 5.7)
Eye, Brain and Other Nervous System	30	(63)	2.0	(0.9, 4.6)
Brain	24	(67)	2.3	(0.9, 6.0)
Endocrine Glands	20	(55)	1.4	(0.5, 3.8)
Hematopoietic Tissue	37	(68)	2.4	(1.1, 5.2)
Other	5	(80)	4.6	(0.5, 108.7)

*Missing values for father's smoking
†For comparison 47% of 438 controls were exposed to father's smoking
‡Sex specific comparison 48% of 288 female controls were exposed
§Sex specific comparison 43% of 150 male controls were exposed

Crude estimates of relative risk for cancers at specific sites in relation to father's smoking are shown in Table 3. The RR for "smoking related" (RR = 1.6) and for "not smoking related" sites (RR = 1.4) are similar. Specific sites with elevated RR included cervix, brain, and hematopoietic tissue.

The RR of 1.7 for cervical cancer among individuals whose fathers smoked is unaffected by adjustment for age, race, sex, maternal smoking, individual smoking, or spouse smoking. The two-fold increase in risk for brain tumors in relation to paternal smoking is similarly unaffected by adjustment for potential confounding variables. Although the number of lung cancer cases with data on father's smoking is small (n = 13), the crude RR for lung cancer associated with father's smoking is 1.8, and is 2.5 after adjusting for age and individual smoking. The RR remains elevated when smoking by spouse and mother are also taken into consideration.

Leukemia and lymphoma risk is also not substantially changed by adjustment for age, sex, race, spouse smoking, and individual smoking. The adjusted RR is 2.5. However, the risk is greater for individuals whose mothers also smoked (RR = 3.1 vs 1.8 for individuals whose mothers did not smoke) and the RR is 1.9 (95 per cent confidence limits = 0.9, 4.4) after adjusting for maternal smoking. For specific hematopoietic cancers, the crude RR was elevated for Hodgkins disease (RR = 5.7, 95 per cent confidence limits = 1.2, 38.4), non-Hodgkins lymphomas (RR = 1.6, 95 per cent confidence limits = 0.6, 4.3), and for acute leukemias (RR = 4.6, 95 per cent confidence limits = 0.6, 34.2).

Individual Smoking Status

Overall and site specific relative risk estimates are shown separately for individuals who smoked and those who never smoked in Table 4. Relative risk estimates in relation to mother's smoking are similar for smokers and nonsmokers and are close to one for all sites but hematopoietic tissue. Increased cancer risk related to father's smoking is not limited to smokers or nonsmokers, although the RR for all sites combined is greater among smokers.

Dose-response

The elevated risks for all cancers combined and for most specific sites were related primarily to father's smoking. However, for leukemia and lymphoma there is an increase in risk when both parents smoked. The RR is 1.7 when one parent smoked and 4.6 if both parents smoked (Mantel-Haenszel chi for trend = 3.25, $p < 0.001$). For both mother's and father's smoking, overall cancer risk increased only slightly with reported frequency of smoking in the house. Risk also tended to increase with reported number of cigarettes smoked, but a large proportion of missing values make these data unreliable.

Discussion

We have found overall cancer risk to be increased among the offspring of men who smoked. There was only a

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TABLE 4—Cancer Risk from Parental Smoking among Nonsmokers and Smokers, All Sites Combined and Selected Sites†

Site	Maternal smoking						Paternal smoking					
	Nonsmokers			Smokers			Nonsmokers			Smokers		
	No.	(% exposed)‡	RR	No.	(% exposed)‡	RR	No.	(% exposed)§	RR	No.	(% exposed)§	RR
All Sites	191	(12)	1.2	227	(19)	1.0	173	(49)	1.2	205	(62)	1.7
"Smoking Related"	47	(9)	0.8	84	(15)	0.8	41	(56)	1.7	79	(59)	1.5
Not "Smoking Related"	144	(13)	1.3	143	(20)	1.1	132	(46)	1.1	126	(64)	1.8
Lip, Oral Cavity, and Pharynx	0	—	—	17	(12)	0.6	0	—	—	17	(53)	1.1
Digestive System	13	(8)	0.7	18	(11)	0.6	12	(50)	1.3	18	(67)	1.7
Respiratory System	4	(25)	2.9	18	(11)	0.6	4	(50)	1.3	18	(50)	1.0
Lung	1	(0)	0.0	14	(14)	0.7	1	(100)	∞	12	(58)	1.4
Bone, Skin, and Connective Tissue	19	(11)	1.0	17	(6)	0.3	20	(30)	0.6	14	(36)	0.6
Breast	29	(10)	0.9	24	(21)	0.9	28	(43)	0.9	23	(61)	1.4
Female Genital Tract	72	(11)	1.0	61	(25)	1.2	59	(51)	1.3	54	(70)	2.2
Cervix	40	(8)	0.7	40	(23)	1.3	34	(56)	1.7	36	(67)	2.0
Eye, Brain and Other Nervous System	17	(6)	0.5	20	(15)	0.8	15	(53)	1.5	15	(73)	2.8
Brain	11	(9)	0.9	20	(15)	0.8	9	(56)	1.7	15	(73)	2.8
Endocrine Glands	11	(18)	1.9	10	(20)	1.1	11	(55)	1.6	9	(56)	1.3
Hematopoietic Tissue	19	(21)	2.3	22	(41)	3.1	17	(65)	2.4	20	(70)	2.4

†Sites with 15 or more cases.
‡For comparison, 11% of 220 nonsmoking controls and 18% of 235 smoking controls exposed to mother's smoking.
§For comparison, 43% of 211 nonsmoking controls and 50% of 227 smoking controls exposed to father's smoking.
‖Sex specific comparison: 45% of nonsmoking controls exposed to father's smoking and 11% exposed to mother's smoking; 52% of smoking controls exposed to father's smoking and 22% exposed to mother's smoking.

small increase in risk associated with maternal smoking. Increased risk associated with father's smoking did not appear to be explained by differences in such factors as age, race, sex, social class (as measured by education and occupation), or smoking habits of the case or control. The effect was not limited to known smoking related sites. Estimated relative risks associated with father's smoking tended to be greater for smokers, males, and non-Whites. We have previously reported an increased cancer risk for individuals married to smokers,[29] but the apparent effect of paternal smoking is not altered by adjustment for smoking by spouse.

Several findings from different sources support the plausibility of increased cancer risk from early life exposure to cigarette smoke. In addition to the experimental studies[1-9] and biochemical studies in humans,[10-21] limited support for the results of the present study can be found in other epidemiologic studies.[22-24,27] Only one of these studies, however, has reported on cancer risk during adulthood from exposure to parent's cigarette smoke.[27]

Stewart, *et al*, in a large case-control study, found a very small (RR = 1.1) increased risk for cancer in children up to age 10 whose mothers smoked.[34] An increased cancer risk related to father's smoking was not seen (RR = 1.0), but 10 years may have been too soon to detect an effect. Neutel and Buck[22] found an increased risk (RR = 1.3) in a prospective study of cancer risk through age 10 among children whose mothers smoked during pregnancy, but did not report on father's smoking.

Questions on parental smoking during pregnancy have been included in a number of case-control studies of particular childhood tumors. Our finding of a two-fold increase in risk for brain cancer among individuals whose fathers smoked is consistent with the data of Preston-Martin, *et al*.[23] In their study, which focused on exposure to nitrosamines, an increased risk of brain cancer (RR = 1.5) among children whose fathers smoked during the mother's pregnancy was seen. Sidestream cigarette smoke which is passively inhaled is one source of exposure to nitrosamines and other N-nitroso compounds.[28] Gold, *et al*, did not report on father's smoking but found a five-fold increase in risk for brain tumors among children whose mothers continued to smoke in pregnancy.[35]

Findings from a study by Grufferman, *et al*,[24] are consistent with our finding of a predominantly paternal effect. In that study, an elevated relative risk for rhabdomyosarcoma was associated only with father's smoking. Manning and Carroll reported no increased risk for childhood leukemia related to mother's smoking.[23] Father's smoking was not reported. Although the number of cases was small and dose-response data were inconsistent, Neutel and Buck did find that the offspring of smoking women had nearly twice the leukemia risk of offspring of women who did not smoke.[22]

Despite the small number of lung cancer cases included, we chose to look at lung cancer risk in relation to paternal smoking because of continued interest in passive smoking and cancer risk at this site.[27,36,37] The RR for lung cancer among individuals whose fathers smoked was 2.5 after adjusting for age and individual smoking. The adjusted RR associated with mother's smoking was 1.8, but this was based on only two smoking mothers among 15 cases. Correa, *et al*, reported an RR of 1.7 for lung cancer associated with mother's smoking, but no increased risk related to father's smoking.[27]

Our finding of a possible cervical cancer risk related to father's smoking has not been reported elsewhere. There is, however, growing support for a role of passive smoking (as measured by spouse smoking) in cervical cancer risk.[38,39]

Data on parental smoking were obtained retrospectively from offspring who may not be in a position to provide accurate histories. Parents or siblings of study subjects were

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also interviewed regarding the smoking histories of the parents to validate the data obtained from subjects. We interviewed 649 relatives of subjects included in this report. Of these, 55 per cent were mothers and 40 per cent were siblings. For more than 350 subject-mother pairs, agreement on qualitative smoking questions ranged from 93 to 98 per cent and was substantially better than chance. There was also good agreement between subjects and their siblings.

Our findings are not due to any obvious recall bias. The hypothesis that parental smoking may cause cancer is not generally well known and study subjects and interviewers were told only that we were interested in smoking patterns in families. We obtained similar responses from mothers and subjects, regardless of case status, suggesting that differential recall probably did not occur.

It is difficult to distinguish transplacental and passive childhood exposures in an epidemiologic study: women who smoke during pregnancy generally continue smoking after the baby is born.[40] Father's smoking may produce transplacental as well as passive childhood exposure.[13,16,20] An effect of father's smoking on genetic material in sperm is also a possibility.[41–45] Only 16 per cent of the smoking mothers in our study began smoking after pregnancy, and no mothers smoked only during pregnancy. This made it difficult to compare cancer risks for individuals exposed in utero with risk in individuals exposed only passively in childhood. Furthermore, 94 per cent of the smoking fathers smoked both before and after the subject's birth.

Nevertheless, if an increased risk were seen for mother's but not father's smoking, a transplacental effect might be a reasonable explanation. In this study and others,[23,24] increased risks were generally related to father's smoking only. Little increased risk was associated with mother's smoking, suggesting a passive rather than a transplacental mechanism. Our failure to find a similar effect for mother's smoking might be due to the fact that they smoked fewer cigarettes than fathers or smoked different types of cigarettes. Although children may spend more time with their mothers than with their fathers, it is also conceivable that mothers do not smoke when actively engaged in child care activities.

The increasing frequency of women smoking after the 1920s should provide future studies with increasing power to detect any late effects of maternal smoking on offspring. The first sizable cohort of individuals exposed to maternal smoking is only beginning to reach the age at which cancer most commonly occurs.

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Mortality Rates in Boston (and Other Large Cities), 1911

Boston's death rate for 1911 was 17.1, which is high compared with rates of most other large American cities.

The 1911 rates for the other cities having over 500,000 inhabitants were—Cleveland 13.55; Pittsburgh 14.94; Chicago 14.55; New York 15.22; St. Louis 15.36; Philadelphia 16.51; and Baltimore 18.43.

A brief analysis of these rates is desirable.

Typhoid Fever:—*From typhoid Boston had the lowest rate of all the cities. The rates per 100,000 were as follows:—Boston 9.14; Chicago 10.78; New York 10.99; Philadelphia 14.11; Cleveland 14.46; St. Louis 15.56; Pittsburgh 25.81; and Baltimore 27.28.*

Scarlet Fever:—*The rates were Baltimore 7.79; Pittsburgh 9.95; Boston 10.74; Philadelphia 11.33; New York 13.25; Chicago 21.20; St. Louis 27.26; and Cleveland 31.12.*

Diphtheria:—*The rates were Baltimore 12.05; St. Louis 16.84; Boston 18.00; Cleveland 21.94; Pittsburgh 23.60; New York 25.84; Philadelphia 31.51; and Chicago 39.11.*

Measles:—*The rates were Chicago 5.75; Cleveland 6.63; Pittsburgh 9.59; Boston 10.74; New York 13.25; Baltimore 13.63; St. Louis 15.84; and Philadelphia 19.30.*

Whooping Cough:—*The rates were Chicago 2.45; St. Louis 4.57; Philadelphia 7.34; New York 7.75; Baltimore 8.50; Cleveland 14.80; Boston 15.68; and Pittsburgh 19.54.*

Taking all these diseases together, Boston had the lowest rate with 64.30 per 100,000; the others in order were Baltimore 69.25; New York 70.88; Chicago 7.29; St. Louis 80.07; Philadelphia 83.59; Pittsburgh 88.49; and Cleveland 88.95.

Tuberculosis of the Lungs:—*The rates per 100,000 were Cleveland 121.77; Pittsburgh 130.88; St. Louis 135.29; Boston 154.88; Chicago 165.98; New York 177.39; Philadelphia 187.31; and Baltimore 205.12.*

This analysis of the communicable diseases should be extremely gratifying to the people of Boston. However, it fails to reveal the reason of Boston's higher rate. But a study of the figures for 1910, for which year more complete figures are available, will show much more. . . .

Cancer, cerebral hemorrhage, organic diseases of the heart, pneumonia and violent deaths stand out as the principal causes which have comparatively high rates in Boston. . . .

There are two reasons why Boston has such a large number of deaths of non-residents. First it has a population in its immediate suburbs greater than the population of the city itself. These people labor in Boston and when ill come to Boston hospitals. The other reason is that Boston is the recognized medical centre for all New England and attracts those afflicted with cancer, for example, a disease more prevalent in the New England States than in any of the other registration states.

Moreover in 1910 Boston had a larger percentage of its deaths over 6 years of age than any of the cities under consideration. In a word, Boston is an old city and has many old people. . . .

But in a word it may be safely said that Boston's high rate is largely due to its geographical position in the centre of populous suburbs, and to its fame as a medical centre, and not, as has been so often intimated, to the unhealthful conditions in the city.

—Davis WH: Boston's death rate. Am J Public Health 1912; 2:638–640.

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Preliminary Communication

CUMULATIVE EFFECTS OF LIFETIME PASSIVE SMOKING ON CANCER RISK*

DALE P. SANDLER ALLEN J. WILCOX
RICHARD B. EVERSON

Epidemiology Branch, Biometry and Risk Assessment Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

Summary Cancer risk from cumulative household exposure to cigarette smoke was evaluated in a case-control study. Overall cancer risk rose steadily and significantly with each additional household member who smoked over an individual's lifetime. Cancer risk was also greater for individuals with exposures during both childhood and adulthood than for individuals with exposures during only one period. These trends were observed for both smoking-related and other sites. These findings are preliminary and must be confirmed with other studies. Nonetheless, they suggest that effects of exposure to the cigarette smoking of others may be greater than has been previously suspected.

INTRODUCTION

INCREASED risk of respiratory illness in children,[1-3] changes in respiratory function in children and adults,[4,5] risk of childhood tumours,[6-8] and risk of lung cancer and possibly other adult cancers[9-14] have all been reported as possible effects of exposure to other people's cigarette smoke (passive smoking). Adult cancer risk from childhood exposure to parents' smoking has also been discussed.[14,15] These studies considered the independent effects of exposure in one period to cigarette smoke from only one source, even though individuals may be exposed to a number of sources over their lifetime.

In a study of adult cancer risk related to parents' smoking[15] we collected data on exposure to cigarette smoke of not only parents, but also spouses and other household members. In the present study cancer risk in relation to cumulative passive exposure to cigarette smoke was examined. We did not collect data on exposures outside the home, but were able to consider whether cancer risk increases with the number of household members who smoke.

METHODS

Study methods have been reported elsewhere.[13,15] Cancer patients were selected from a hospital-based tumour registry. They included all those with cancer diagnosed between July 1, 1979, and March 31, 1981, and assumed to be alive on March 31, 1981. Patients ranged from 15 to 59 years of age at the time of diagnosis, and all cancer sites except basal-cell cancer of the skin were included. Patients were restricted to age 59 and younger to maximise the likelihood of maternal smoking, since few women were smokers before 1920.

Of 740 eligible cancer patients identified from the tumour registry, 107 (14%) died before we could contact them. An additional 115 (16%) either refused to participate or could not be contacted. 518 (70%) patients completed questionnaires. Control subjects were cancer-free and of the same race, sex, and age (±5 years) as patients. They were friends or acquaintances of patients (n = 309) or were randomly selected by systematic telephone sampling (n = 209). Patients and control subjects were also similar in occupational category and smoking habits. Analysis was restricted to individuals who lived with both natural parents for most of the first 10 years of life. Results are reported for 369 patients and 409 control subjects who supplied information about the smoking habits of their spouse and parents.

Information on exposure to cigarette smoke was obtained by means of a structured questionnaire that was sent to all subjects. Another questionnaire was sent and follow-up telephone calls were made when a response to the first questionnaire was not obtained. Childhood exposure to cigarette smoke was assessed from questionnaire reports of smoking histories of parents and information on other household members who smoked. Subjects were considered to be exposed during childhood if one or both parents smoked cigarettes in the house before the subject was 10 years old or if one or more other household members smoked during that period. Passive exposure to cigarette smoke during adulthood was estimated from the number of years of marriage during which a spouse smoked. Subjects were considered to be exposed if they had a spouse who smoked regularly at any time during their marriage. Active smokers were defined as those who ever smoked as many as 1 cigarette a day for as long as 6 months.

*Some of this material was presented at the annual meeting of the society for Epidemiologic Research, June, 1984, Houston, Texas USA.

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TABLE I—OVERALL CANCER RISK FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE

	Number of household members who smoke			
	0	1	2	3 or more
Combined group				
Patients	54	127	123	48
Control subjects	99	161	97	34
Odds ratio	1·0	1·4	2·3*	2·6*†
Active smokers‡				
Patients	22	60	78	35
Control subjects	38	73	60	25
Odds ratio	1·0	1·4	2·2*	2·4*†
Non-smokers				
Patients	32	67	45	13
Control subjects	61	88	37	9
Odds ratio	1·0	1·5	2·3*	2·8*†

*Statistically significant differences between risk with specified number of exposures and with no exposure, $p<0·05$.
†Statistically significant χ^2 for trend, $p<0·01$.
‡Current smokers and ex-smokers.

We have found[13,15] that exposure to parents' or spouse's smoking contributed independently to cancer risk—ie, adjusting for one exposure did not alter the risk associated with the other. Thus we used two approaches to measure the effects of multiple exposures: cancer risk was examined in relation to the total number of household members who smoked, irrespective of when the exposures occurred, and in relation to the period during which the exposures occurred (childhood or adulthood only, or both periods). Odds ratios were calculated and a chi-square test was used to assess statistical significance. A chi-square test for linear trend was used to evaluate the risk with increasing numbers of exposures in unadjusted[16] and adjusted[17] analyses.

RESULTS

Cancer risk associated with exposure to increasing numbers of household members who smoke is shown in table I. A smoking mother, father, spouse, or 1 or more additional household members who smoked during the patient's childhood or a spouse who smoked while married to a patient each counted as one exposure. The total number of exposures is the sum of the individual exposures. Overall cancer risk increased significantly with increasing numbers of exposures, with odds ratios rising from 1·4 for 1 exposure to 2·3 for 2 exposures and 2·6 for 3 or more exposures. Statistically significant linear trends were also seen when smokers and non-smokers were considered separately. Adjustment for potential differences in age, race, sex, and educational level did not alter these trends.

TABLE II—OVERALL CANCER RISK FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE IN CHILDHOOD AND ADULTHOOD

	Age period of exposure			
	No exposure	Childhood only*	Adulthood only†	Both
Patients	54	107	58	145
Control subjects	99	124	72	98
Odds ratio	1·0	1·6‡	1·5	2·7‡§
		1·5‡		

*Exposure to smoking mother, father, or other household member during childhood.
†Exposure to smoking spouse.
‡Statistically significant differences between risk with specified exposure and no exposure, $p<0·05$.
§Statistically significant linear trend: no exposure, exposure in only one time period, exposure in both time periods, χ^2 for trend = 23·7, $p<0·01$.

We also measured cancer risk in relation to the period when exposures occurred (table II). Risk rose by 60% for individuals exposed during childhood only and by 50% for individuals exposed during adulthood only but was more than doubled for those exposed during childhood and adulthood (odds ratio = 2·7). There was a significant linear trend in risk for individuals exposed in no, 1, or 2 periods. Again trends were similar for smokers and non-smokers and were not affected by adjustment for potential confounding factors.

TABLE III—CANCER RISK FROM MULTIPLE HOUSEHOLD EXPOSURES TO CIGARETTE SMOKE: SITES WITH 15 OR MORE CASES*

Site	Number of cases	Number of exposures			
		0	1	2	3 or more
All sites	369	1·0	1·4	2·3	2·6‡
Smoking related†	115	1·0	1·8	3·0	3·8‡
Other	254	1·0	1·5	2·4	2·6‡
Buccal cavity and pharynx	15	1·0	4·9	5·1	2·9
Digestive tract	30	1·0	0·7	1·8	1·3
Respiratory tract	19	1·0	0·7	0·6	2·9
Breast	48	1·0	2·0	2·4	3·3‡
Cervix	62	1·0	1·6	3·6	3·4‡
Eye, brain, and other nervous system	29	1·0	2·3	2·3	0·7
Thyroid	19	1·0	1·0	3·1	8·7
Leukemia and lymphoma	37	1·0	2·5	5·1	6·8‡

*Odds ratios are given.
†Includes oral cavity and pharynx, oesophagus, pancreas, respiratory tract, urinary tract, and cervix.
‡Statistically significant linear trend.

Cancer risk increased with increasing numbers of household exposures to cigarette smoke for smoking-related sites and for other sites that are not thought to be smoking related (table III). Smoking-related sites included cancers of the oral cavity and pharynx, oesophagus, pancreas, respiratory tract, urinary tract, and cervix.[13,18] For smoking-related sites odds ratios for 1, 2, and 3 or more exposures were 1·8, 3·0, and 3·8, respectively. The trend for the other sites combined was also statistically significant but the risk was less than that for smoking-related sites. The trends for cancers of the breast and cervix and for leukaemia and lymphoma combined were significant, but the trend for cancer of the respiratory tract was not.

DISCUSSION

If passive smoking has an effect on cancer risk the nature and extent of that risk are likely to differ for childhood and adult exposures. The clear overall trends found in this study might be associated with carcinogens present in tobacco smoke acting through multiple mechanisms at different periods of life. We found the risk of all cancers increased steadily and significantly with cumulative lifetime exposure to household members who smoke. This trend was not altered when adjustment was made for confounding variables.

Our findings must be regarded as preliminary. Prompted in part by experimental evidence[19] we initially intended to measure the effect of transplacental or early childhood exposure to carcinogens on cancer risk in adulthood. We chose to investigate cigarette smoke because exposure to this carcinogen is both common and measurable. The finding of a cumulative lifetime risk from passive smoking was unexpected.

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We collected information on most possible sources of cigarette-smoke exposure that would be encountered during childhood but the only adult exposure we considered was that resulting from the smoking of a spouse. We did not validate information on smoking habits of spouses but interviewed more than 700 relatives of patients and control subjects to validate the quality of parental smoking histories provided by adult offspring. Study subjects provided adequate information on parents' smoking, and the quality of these data did not differ between patients and control subjects.

For adults in the United States exposures to cigarette smoke outside the home may be important.[20] Also the frequency of exposure to other people's cigarette smoke may change with age, with the peak exposure possibly occurring during a person's 20s.[20] We did not take exposures outside the home or age-related changes in exposure frequency into account.

Our data are limited by small numbers of any specific cancer site, by certain characteristics of our study sample, and by other features of our method.[13,15] No conclusions about the impact of passive smoking relative to the effects of direct smoking can be made, since the selection of friends as control subjects meant they were usually matched with patients on smoking status. We confirmed the quality of our data and ruled out many, but not all, potential confounding factors.

Although the passive smoker receives a quantitatively lower exposure than the active smoker, that exposure is qualitatively richer in many smoke constituents: there is 3 times as much benzo(*a*)pyrene, 6 times as much toluene, and more than 50 times as much dimethylnitrosamine in a fixed volume of sidestream smoke in the gas phase as there is in cigarette smoke inhaled by the active smoker.[18] The potential for damage from passive exposure may be greater than has been previously recognised.

Our finding of dose-dependent cancer risks for sites not considered to be related to active smoking might be questioned because active smokers are also passively exposed. For some sites it is not clear in the literature if no risk from direct smoking exists or if a possible link has not yet been investigated. For other sites, such as the breast, some studies have found no cancer risk associated with smoking.[21] One possible explanation for this discrepancy is that in studies comparing smokers with non-smokers, passive smokers are included in the non-smoking group. This would make it difficult to detect a small difference in risk due to smoking. Few studies have evaluated the effects of passive smoking on risk of cancer at sites other than the lung. Furthermore, there is little data available on the effects of transplacental or childhood exposure to cigarette smoke on cancer risk in adulthood.

Data from biochemical and experimental studies support our findings though many of these reports must be regarded with caution. There is evidence that non-smokers are exposed to potential carcinogens through the cigarette smoking of others. Cigarette-smoke by-products such as cotinine and thiocyanate have been measured in the blood, urine, and saliva of non-smoking adults, children, and fetuses exposed to smokers,[22-26] and there has been at least one report of raised levels of mutagens in urine of passive smokers.[27] Greater activity of enzymes that metabolise benzo(*a*)pyrene has been noted in placentas of smokers[28-30] and even passive smokers.[31] Similar increases may occur in tissues of fetuses, children, or adults exposed to smokers.

Studies in laboratory animals provide evidence in support of an adult cancer risk from transplacental or childhood exposure to cigarette smoke, but this hypothesis has not been tested directly.[19] Data from these studies show that many carcinogens, including those in cigarette smoke, are active when administered transplacentally or during early life and may produce effects at lower doses than those required for adults.[32-36] Some low-dose exposures which are not in themselves carcinogenic increase the sensitivity of exposed animals to later carcinogenic exposures.[37,38] In other experiments tumours resulting from transplacental and early postnatal exposures were not apparent until the animals were fully developed and did not necessarily differ in site or morphology from spontaneously occurring tumours.[32,39] This is consistent with our finding of raised risk for adult tumours at many sites.

Future studies should include cancer sites not necessarily associated with active smoking and should take into account childhood sources of passive smoke exposure.

Correspondence should be addressed to D. P. S, Epidemiology Branch, NIEHS, PO Box 12233, Mail Drop A3-02, Research Triangle Park, NC 27709 USA.

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It is unclear whether the result in the youngest cohort can be explained by aggressive tumour growth, by too low a sensitivity of the mammographic test, by too short a follow-up, or by chance. The absence of any effect so far in the youngest age-group corresponds with the early results of the age-group 40–49 at entry in the Health Insurance Plan (HIP) trial. 5 years after the HIP screening programme had begun, the number of breast cancer deaths was 19 in the study group and 20 in the control group (RR = 0·95).[3] 10 years after the start the RR was 42/54 (0·78), and 14 years after the start it was 46/61 (0·75).[4] Nevertheless the HIP investigators hesitated to accept this finding as evidence of the effectiveness of screening under age 50.

In Nijmegen a disease stage classification system according to mammographical and/or histopathological tumour size was used. "Advanced stage" means that the axillary lymph nodes were histologically involved or that the lesion consisted of infiltrative carcinoma and was at least 2 cm in size. In the age-group 35–49 at diagnosis 38% of 40 screen-detected cases had advanced disease stage, as opposed to 4 out of the 6 cases in women who did not participate in the screening programme. According to these figures a subsequent mortality reduction can be expected in the youngest age-group.

Finally, attention should be paid to the weak effect of screening on breast cancer mortality in the oldest age-group. It is assumed that breast cancer grows rather slowly in this group.[5,6] As a consequence, the lead-time should be very long, and a strong effect could be expected after a longer period of follow-up. The odds ratio for the birth cohort born before 1910 is now only 0·81. Maybe this RR estimate is weak because of different underlying mortality risks (independent of any screening effect) in the participating and non-participating groups. Maybe differences in patient's delay explain that the effect was less favourable than expected. And maybe selective misclassification of the death certificates is another explanation. Further studies will focus on these potential biases.

Departments of Social Medicine, Radiology, and Pathology, University of Nijmegen, 6525 EJ Nijmegen, Netherlands
A. L. M. VERBEEK
J. H. C. L. HENDRIKS
R. HOLLAND

Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen
M. MRAVUNAC

Department of Epidemiology, University of Limburg
F. STURMANS

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LIFETIME PASSIVE SMOKING AND CANCER RISK

SIR,—Dr Sandler and colleagues (Feb 8, p 312), in a preliminary report, describe the relative cancer risk for persons living in households with 0, 1, 2, and 3 or more members who smoke. The risk increased, both for active and for non-smokers, with the number of household members who smoked, and Sandler et al suggest that exposure to ambient smoke in the household might be responsible.

In table I they normalise the odds ratio for cancer risk to unity for households with no (other) smokers and disregard exposure to cigarette smoke outside the home. Calculating to two decimal places, the odds ratios for households with 1 (other) smoking member are 1·42 for active smokers and 1·45 for non-smokers; for households with 2 (other) smokers the corresponding ratios are 2·25 and 2·32; and for 3 or more, the ratios are 2·42 and 2·75. The risk ratios for active smokers are therefore, within the error limits, the same as for non-smokers; to simplify the argument, I shall treat them as identical.

Suppose the average risk of cancer is N from all causes unconnected with smoking, A from active smoking, and P from passive smoking. An active smoker is also a passive smoker of his own ambient cigarette smoke, so the total cancer risk for active smokers in households with no other smoker is N + A + P; in households with 1 other smoker the risk is N + A + 2P. For non-smokers, the corresponding risks are N and N + P. Because the data of Sandler et al imply that odds ratios (and hence the ratios of relative risks) are virtually identical we require that $(N + A + 2P)/(N + A + P) = (N + P)/N$. In other words A + P = 0. This same relation is obtained from relative risks in households with 2 and with 3 or more (other) smokers. A multiplicative model, in which the cancer risk in, for example, an active smoker in a household with no other smokers is of the general form, $N(1 + A + P)$, where A and P are now proportional to the concentration of effective carcinogens in active and passive smokers, respectively, also yields the same equality.

The relation A + P = 0 leaves us with three possible interpretations:

(1) Active and passive smoking are both non-carcinogenic (A = P = 0). (2) Active smoking is carcinogenic and passive smoking is prophylactic (A = − P). (3) Active smoking is prophylactic and passive smoking is carcinogenic (P = − A).

The statistical uncertainty in Sandler's table I is large enough to permit slightly less paradoxical inferences, but let us pursue the unthinkable a little further.

Three randomised controlled intervention trials (the Oslo study,[1] the Whitehall study[2] and MRFIT[3]) provide a direct epidemiological test of the hypothesis that giving up active smoking reduces the risk of cancer. In the "intervention" (low-smoking) groups in these three trials together there were (including registrations as well as deaths in the Whitehall study[2]) 149 cancers in a combined entry population of 7746 (1·92%); while in the relatively high-smoking control groups there were 121 cancers in 7797 (1·55%). From the orthodox viewpoint—namely, active smoking causes at least 30% of all cancers—these findings are as paradoxical as the inferences from Sandler's study. We might just be able to postulate complicated, though implausible, causal models to account for Sandler and colleagues' table 1, or we may put those results on one side because of their preliminary character. It is more difficult to evade the implication of the methodologically reputable randomised trials: active cigarette smoking has little or no net carcinogenic action.

Department of Medical Physics, University of Leeds, General Infirmary, Leeds LS1 3EX
PHILIP R. J. BURCH

1. Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. *Lancet* 1981; ii: 1303–10.
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SIR,—Dr Sandler and colleagues' paper on the cumulative effects of lifetime passive smoking on cancer risk appears seriously flawed. They compared 518 out of a total of 740 cancer patients aged 15–59 from a hospital-based tumour registry, with 518 controls of the same age, sex, and race. 309 controls were friends or acquaintances of the patients and 209 were randomly selected by systematic telephone sampling. Results are presented for 369 (70%) cases and 409 (79%) controls. Apart from death before the subjects could be contacted and refusal, only those persons who had "lived with both natural parents for most of the first ten years of life" were analysed. We are told that they supplied information about the smoking habits of their spouse and parents. Presumably, they also supplied information about their own smoking.

The results are shown in three tables, only one of which differentiates between active and passive smoking, and none of which differentiates between sex, age, and race. The belief that these factors do not matter because they were matched for is unsound. The reader has no idea how differences between those

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initially chosen and those finally analysed could have influenced the results. Moreover, as soon as the groups are stratified by active smokers and never smokers, the matching is broken. Until the results have been presented for non-smokers by age, sex, and race no conclusions can be drawn.

Furthermore the truncated age group (15–59 years) has resulted in an unrepresentative selection of cancer cases. Even so, the distribution by cancer site seems strange: there were 62 (17%) cancers of the cervix uteri but only 19 (5%) cancers of the respiratory tract and 48 (13%) breast cancers. The trend in cancer risk from multiple household exposures to cigarette smoke is least impressive for cancer of the respiratory system, where an effect might be expected to be greatest, and most striking for leukaemia and lymphoma where any biological explanation is, to say the least, obscure. The most extraordinary finding appears to have been the very similar trends in cancer risk with number of household members who smoke irrespective of whether the cases smoked or not. Indeed, Sandler and colleagues' publication on the same material in the *American Journal of Epidemiology* (1985; **121**: 37–48) shows that the effect of passive smoking on cancer risk appears to have been greater than the effect of active smoking.

School of Public Health,
University of Michigan,
Ann Arbor, Michigan 48109, USA IAN HIGGINS

**These letters have been shown to Dr Sandler and colleagues, whose reply follows.—ED. L.

SIR,—Professor Burch presents an algebraic rearrangement of our data that suggests that smoking is protective. His approach assumes that childhood and adulthood exposures are interchangeable. As we indicated in our paper, the apparently linear trends in table I simplify a complex set of relationships. Our data illustrate that childhood and adulthood exposures may contribute independently to cancer risk in adulthood, but this does not imply that these two exposures are equivalent. Data we present elsewhere suggest the two risks may, in fact, be different (ref 1, and unpublished). As shown in the accompanying expansion of table II, the odds ratio associated with passive exposure only as an adult was 1·8 for non-smokers but only 1·2 for active smokers (not equal, as Burch's analysis requires). For childhood exposures, the opposite was true: the odds ratio was 1·9 for smokers and 1·3 for non-smokers. Thus, passive exposure in childhood seems to have its greatest effect among persons later exposed to a carcinogen (their own smoking), while passive exposure in adulthood has its largest effect among persons not actively exposed. In short, our data do not support the simplified biological assumptions Burch requires for his analysis.

Dr Higgins raises concern about possible biases in the study and requests additional data. The information he seeks is provided in a paper he cites.[1] As explicitly stated in both papers, there was no confounding by the variables mentioned by Higgins. The "truncated" age group was chosen because a primary aim of our study was to evaluate effects of mothers' smoking. Since few women smoked before 1920, we studied cases who were younger than age 60 in 1980. It will be several years before cancer risk associated with mothers' smoking can be evaluated for older persons. The distribution of cancer sites studied resulted from methodologic decisions and hospital referral patterns which were discussed in the papers. Nonetheless this group was not preselected on the basis of any prior hypothesis, and it is not easy to see how inclusion of more cancers that are "unrelated" to cigarette smoking would lead to an inflated overall cancer risk from passive smoking.

Higgins cites our finding of a leukaemia effect as one for which "any biological explanation is, to say the least, obscure". On the contrary, cigarette smoke contains chemicals known to be leukaemogenic, and has been associated with increased leukaemia risk in many,[2–5] although not all[6] studies. Some of these studies find an apparent dose-response, especially for non-lymphocytic leukaemias.[2,3,5] The 40–50% increase in leukaemia risk among smokers is much smaller than that reported for other sites such as the lung, which may account for the lack of interest in smoking and leukaemia. Experimental and biochemical data from a variety of sources (refs 7 and 8, and discussed in our papers) are also consistent with a possible association between leukaemia risk and exposure to cigarette smoke.

There is one final point. Our study was not designed to compare the effects of active and passive smoking. Our method of choosing friend controls inadvertently matched for active smoking, which erases the possibility of observing an effect due to active smoking. Higgins' comparison of the effects of active and passive smoking is not meaningful in our data.

The questions raised by Burch and Higgins do not persuade us that our study is "seriously flawed". We stress the need for additional studies and strongly urge investigators to consider that the range of possible effects from active and passive exposure to cigarette smoke may be broader than has been thought.

National Institute of
Environmental Health Sciences,
Research Triangle Park,
North Carolina 27709, USA D. P. SANDLER
A. J. WILCOX
R. B. EVERSON

OVERALL CANCER RISK FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE IN CHILDHOOD AND ADULTHOOD

	No exposure	Age period of exposure: Childhood only*	Age period of exposure: Adulthood only†	Both
Active smokers				
Patients	22	63	25	92
Controls	38	58	37	65
Odds ratio	1·0	1·9¶	1·2	2·4‡,§
		1·6		
Non-smokers				
Patients	32	44	33	53
Controls	61	66	35	33
Odds ratio	1·0	1·3	1·8‡	3·1‡,§
		1·5		

*Exposure to smoking mother, father, or other household member during childhood.
†Exposure to smoking spouse.
‡Significant differences between risk with specified exposure and no exposure ($p<0·05$).
¶$p=0·05$.
§Statistically significant linear trend: no exposure, exposure in only one time period, exposure in both time periods (χ^2 for trend, $p<0·01$).

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REDUCED RESPONSE OF URAEMIC BLEEDING TIME TO REPEATED DOSES OF DESMOPRESSIN

SIR,—Treatment with desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) shortens prolonged bleeding times in patients with von Willebrand disease,[1] platelet defects,[2] and uraemia,[3–5] and in healthy subjects.[2] The bleeding time correction by desmopressin has been attributed to the raising of plasma concentrations of high-molecular-weight forms of factor VIII (FVIII) related antigen and von Willebrand factor (vWF) activity.[6] In uraemia FVIII-vWF concentrations are normal to high even before desmopressin; here, the presence of abnormal multimers may explain why normal multimers, provided via desmopressin[5] or cryoprecipitate[5–7] are effective.

Published experience with desmopressin in uraemia is limited to short-term responses. When we gave cryoprecipitate (30 ml/kg) in

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of urease; all these specimens yielded a heavy growth of *C pyloridis*. One-third of tests were positive by 3 h and half by 6 h.

The advantage of this rapid test is the achievement of a diagnosis of *C pyloridis* gastritis on the same day that patients attend for endoscopy, thus avoiding a second hospital appointment. We have found this very useful for the enrolment of patients into a therapeutic trial comparing medications.

We thank our colleagues for obtaining the biopsy samples.

Department of Medical Microbiology,
Dudley Road Hospital,
Birmingham B18 7QH

CLODNA A. M. MCNULTY
R. WISE

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CAMPYLOBACTER PYLORIDIS IN PEPTIC ULCER

SIR,—We read with interest Dr Rathbone and colleagues' letter (May 25, p 1217) in response to our April 20 report and apologise for our failure to make it clear that all peptic ulcer patients were diagnosed by endoscopy and that the sera studied were collected before treatment. The antibody assays were performed under code.

The 50 members of laboratory staff did not undergo endoscopy (for obvious reasons) nor have they been labelled as a reference group. Similar remarks apply to the children's sera, which were a general collection referred to our hospital for viral studies. The purpose of our communication was solely to report the difference found between these cohorts. The data encourage speculation as to a link between *Campylobacter pyloridis* and peptic ulcer. The raised titres in well people may be due to symptomless infection, perhaps a carrier state—this is not unknown in infectious diseases and has provided a stimulus to epidemiologically based studies.

Rathbone et al suggest that under some circumstances a specific gut IgM response might occur without either an IgA or IgG response. This is at odds with generally accepted mechanisms of gut immunity, which regard IgA as the first immunoglobulin of response in the gut.[1]

J. KALDOR
B. DWYER
WEE TEE
PETER MCCARTHY
JAN WATSON

Fairfield Infectious Diseases Hospital,
Fairfield, Victoria 3078, Australia;
and Alfred Hospital,
Prahran

1. Walker WA, Hong R. Immunology of the gastrointestinal tract. Part II. *J Pediatr* 1973; 83: 517–30.

LIFETIME PASSIVE SMOKING AND CANCER RISK

SIR,—Dr Sandler and colleagues (Feb 8, p 312) present results in their table I showing that odds ratios for overall cancer risk increase markedly in relation to the number of household members who smoke, and this increase is similar for active smokers as for non-smokers. Professor Burch (April 13, p 866) comments that this similarity leads to the paradoxical conclusion that the average effects of active smoking and passive smoking must be equal and opposite. In reply, Sandler and colleagues point out that this equality is in reality a superficial averaging of two findings—a greater odds ratio for non-smokers than smokers in relation to passive smoking as an adult, and a greater odds ratio for smokers than non-smokers in relation to passive smoke exposure in childhood. Surely, however, the latter finding is even more implausible than equality of effect in smokers and non-smokers. On any plausible model, the relative effect of passive smoking should be greater in non-smokers, who start from a smaller background level, than in smokers. Mathematically, if β is the background level of risk in the absence of passive smoke exposure and δ the increment in risk resulting from passive smoke exposure, the odds ratio $(\beta + \delta)/\beta$ will tend to be smaller the greater the value of β.

Sandler's findings are implausible in other respects—notably the large effect claimed for passive smoking for a number of cancers (breast, thyroid, leukaemia/lymphoma) that are generally believed to have little or no relationship to active smoking—and attention must inevitably centre on the adequacy of the study methods used. The choice of controls used in this study, a mixture of friends or acquaintances of patients and people randomly selected by systematic telephone sampling, is certainly unusual and seems very open to question. Sandler and colleagues admit that the study cannot be used to relate active smoking to risk of cancer, since estimates will be biased by the similarity of active smoking habits of friends. Surely, since active and passive smoking are strongly correlated, bias in studying the relationship of passive smoking to risk of cancer will also arise.

Bias may also arise because of the difference in method of approach. Thus, in a separate paper,[1] Sandler et al note that the proportion of subjects not answering questions on marital status was over three times greater in controls than in cases. If there are highly significant differences in the proportion of certain questions being answered at all, how does one know that there are not highly significant differences in the way the passive smoking questions are dealt with?

Given that active smokers receive substantial passive smoke exposure from their own cigarettes, it is a priori implausible that passive smoking should increase risk of cancers that are not associated with active smoking. Seen in this light, a much more appropriate analysis of Sandler's data would be to treat patients with smoking-related cancers as cases and patients with non-smoking-related cancers as controls. Calculations from data presented in table III of their *Lancet* paper indicate that there is no significant relation between passive smoking and cancer risk if the data are analysed in this way. This is a more plausible finding, and consistent with the results of my 1984 review[2] which concluded that there is as yet no convincing evidence that passive smoking results in any material risk of serious health hazards.

P. N. Lee Statistics and Computing Ltd,
25 Cedar Road,
Sutton, Surrey SM2 5DG

PETER N. LEE

1. Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985; 121: 37–48
2. Lee PN. Passive smoking. In: Cumming G, Bonsnoore G, eds. Smoking and the lung. Plenum, New York, 1984.

SIR,—In their reply accompanying my letter of April 13 (p 866) Dr Sandler and colleagues misrepresent me as arguing that "smoking is protective". In fact I pointed to three possible interpretations of their findings and concluded that "active smoking has little or no net carcinogenic action". The new breakdown of their findings does not eliminate the paradoxes implicit in the aggregate data.

Department of Medical Physics,
General Infirmary,
Leeds LS1 3EX

P. R. J. BURCH

BENZTROPINE INHIBITS TOXICITY OF MPTP IN MICE

SIR,—The discovery that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes irreversible parkinsonism in man and other primates has provided new clues as to the cause of Parkinson's disease. The ability of MPTP to produce a relatively specific destruction of dopaminergic nigrostriatal neurons can be prevented by inhibitors of the enzyme monoamine oxidase B, including deprenyl, in primates[1,2] and mice.[3] Deprenyl (selegiline hydrochloride) has been in use in Europe for some years as an adjunct to levodopa treatment because of its ability to inhibit dopamine catabolism in the brain. Now it is suggested that early treatment with deprenyl might slow or even prevent progression of Parkinson's disease by preventing toxicity of some MPTP-like substance conceived as responsible for Parkinson's disease.

MPTP is not neurotoxic; its oxidation product MPP^+ (1-methyl-4-phenylpyridine) is.[4] MPP^+ accumulates in nigrostriatal neurons via the dopamine neuronal uptake system; MPP^+ uptake into rat striatal synaptosomes is inhibited by dopamine uptake inhibitors

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Letters to the Editor

RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

It is unfortunate that Sandler et al. (1) did not obtain information on, or account for, additional possible confounding variables in their study. The only ones that they report having included were age, sex, race, active smoking, education, blue collar vs. white collar occupation, and parental smoking. We have found that the amount of passive smoking was correlated with self-reported exposure to occupational hazards, use of marijuana, and alcohol intake (2). Thus, for example, the increased risk of breast cancer observed by Sandler et al. may be due to increased alcohol intake (3) rather than to passive smoking. Perhaps exposure to occupational hazards explains the slightly increased risk of hematopoietic cancer (4) among passive smokers, and husbands' sexual behavior associated with the smoking habit (5) accounts for an increased risk of cervical cancer. The authors alluded to this last possibility, but did not rule it out.

Sandler et al. (1) were careful to point out that the associations that they found "... might relate to other factors we have not measured or to deficiencies in study design." However, they went on to state that they "have not been able to identify a possible confounder . . . that could have caused the difference in smoking patterns of spouses between cases and controls." The above suggestions represent a few possibilities.

Sandler et al. also pointed out that sidestream smoke has higher concentrations of certain carcinogens than mainstream smoke. Nevertheless, because (a) the dosage of smoke is so much lower in passive than in active smoking, and (b) smokers also "passively" breathe sidestream smoke in addition to inhaling mainstream smoke, it would be surprising if passive smoking actually caused any cancers that were not associated with active smoking.

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Gary D. Friedman
Department of Medical Methods Research
Kaiser Permanente Medical Care Program
Oakland, CA 94611

RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

Sandler et al. (1) removed much of the impropriety of their demonstration of an effect of passive smoking generally in raising the risk of cancer by focusing particular attention on the instances in which the study case was a nonsmoker. But substantial impropriety remains.

First, it gives cause to wonder how passive smoking could give rise to a doubled rate of cancer generally, including cancer of sites not previously associated with direct smoking of cigarettes. Those specific sites are only identified in their table giving results for nonsmokers plus smokers combined, with the added risk for passive smoking then shown at 60 per cent. The crude added risk of lung cancer from passive smoking, smokers plus nonsmokers combined, is shown as 90 per cent, but based on only 22 cases of lung cancer—of whom only two were nonsmokers. So only two nonsmoking lung cancer cases were available for judging the true effects of passive smoking on lung cancer.

Elsewhere (2), the study of passive smoking has focused specifically on lung cancer and specifically among individuals who themselves were nonsmokers, i.e., the nonsmoking wives of smokers, and, even so, such studies have been subject to criticism (3).

In Sandler et al. (1), the authors have given ostensible concern for potential confounding factors. Perhaps others would agree that confounding factors have been taken into account, but not in my opinion. The issue of what is a confounding factor has become so confused that I have hesitated to get into the fray. I just look to see what is sensible. (Incidentally, the same issue of the *Journal* does carry an item (4) on confounding).

What the authors (1) treat as confounding factors are age (in broad age categories), sex, race, smoking (not relevant for the analysis on nonsmokers), three broad education groups, two broad occupation groups, and whether either parent smoked. Presumably, the factors adjusted for simultaneously in the analysis of passive smoking among nonsmokers are age, race, sex, and education.

But, somehow, I do not think of age as a confounding factor. Rather, it is a logical factor which must be taken into account in any reasonable analysis if one wants to come up with reasonable results. Much the same is true of race and sex, though I am less certain about level of education.

A truly confounding factor to my mind would be something like smoking and alcohol consumption. If heavy drinkers are also heavy smokers, sorting out their separate effects could be a problem. Anyway, if we are concentrating on passive smoking among non-

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smokers, then we are contrasting families with a single smoker against families where neither spouse smokes. And differences could exist between them. Thus we might ask: 1) Are their alcohol consumption habits the same? 2) What are the differences in their dietary habits? 3) How might they differ in age at first intercourse, frequency of intercourse, circumcision status of husband, etc.? 4) Are numbers of children or pregnancies and ages at first birth or pregnancy the same for single-smoker and nonsmoker families? 5) What true differences may exist in occupations leading to cancer?

These possible correlates of smoking practice might account for the observed differences reported in cancers of a variety of sites, and these are the true potential confounding factors, whether or not we are in a position to get at them. What Sandler et al. have taken as potential confounding factors are just the straightforward factors requiring adjustment that any reasonable epidemiologist would employ.

One particular thing strikes me about the Sandler et al. study. Passive smoking has been shown to double the risk of all cancers among nonsmokers, albeit true confounding factors have not been taken into account. But studies focusing on lung cancer among nonsmokers consequent on passive smoking have also come up with about the same doubling of risk. To other criticisms made of such other studies may be added that they may be overlooking true confounding factors.

The true criticism of passive smoking remains—it is an unpleasant burden to impose on the nonsmoker.

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Nathan Mantel
Mathematics, Statistics and Computer Science
The American University
Bethesda, MD 20814

RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

It is ironic that whereas a few of us agonize over the question of whether active smoking is a major cause of lung cancer others seem willing to believe that passive smoking causes an appreciable incidence of lung and other cancers.

Sandler et al. (1) purport to have studied cancer risk in relation to "passive smoking in adulthood." They did not. They studied cancer cases in active and nonactive smokers in relation, mainly, to the smoking habits of the spouse. Two broad aspects were considered: whether or not the spouse "smoked regularly at any time during their marriage"; and, for dose-response relations, "the number of years of marriage during which a spouse smoked;" or "the average amount smoked by spouse." Also, the "nonexposed group consisted of persons married to nonsmokers and persons who never married."

The smoking habits of the spouse are, however, a very poor surrogate for passive exposure to cigarette smoke. Thus, Repace and Lowrey (2) have estimated that the typical workplace exposure in the United States is about four times the typical exposure in the home. Matsukura et al. (3) found in Japan that the mean (± SE) urinary cotinine excretion for 200 nonsmokers living with no smokers in the home was 0.51 ± 0.09 μg/mg of creatinine; for 272 nonsmokers with smokers in the home it was slightly higher, at 0.79 ± 0.10 (same units), but not significantly so.

The assumption by Sandler et al. that the smoking status of the spouse is a useful measure of exposure to ambient cigarette smoke is, therefore, highly suspect. This doubt is borne out by their own study of lung cancer cases in which "... there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose ..." (1). The observed cancer associations were with the status of the spouse and not with exposure to cigarette smoke. That uncorrected confounding factors might have been present is further suggested by their finding of "statistically significant" associations "with several specific tumor sites ... including some which are not ordinarily regarded as smoking-related."

Assortative mating is a well established phenomenon that extends to the smoking habit (4) and hence we have to consider that the underlying factors leading to the choice of smoking/nonsmoking spouse might associate with the risk of certain cancers.

In principle, randomized trials can of course distinguish between causal, constitutional, and causal-plus-constitutional hypotheses of associations but they have yet to be conducted in connection with passive smoking. However, two important studies have been carried out, with randomization, in the context of active smoking (5, 6) and, because active smokers are inevitably passive smokers as well, the results of these trials are of immense importance not only to the findings of Sandler et al. but also to general theses about the carcinogenicity of mainstream and sidestream tobacco smoke.

We obtain the best available direct epidemiologic test of causal hypotheses by combining the results of the MRFIT in the United States (5) with those of the Whitehall Study in London (6). In the combined, low-smoking intervention groups some 56 cases of lung cancer (deaths in MRFIT, deaths and registrations in the Whitehall Study) were recorded in the total entry group of 7,142 men, a frequency of 0.78 per cent. For the combined, relatively high-smoking "usual care" groups the corresponding numbers were 53 in 7,169 or 0.74 per cent. Findings for all cancers other than lung cancer, several of which associate strongly with cigarette smoking, are astonishing. Some RR cases, or 1:2:1

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per cent, were recorded in the combined low-smoking intervention groups but only 60, or 0.84 per cent, in the high-smoking usual care groups. Is smoking prophylactic? Does quitting smoking result in changes of life-style that cause cancer? Or is this finding a wild, but acceptable, random excursion?

We may not be entitled to estimate confidence limits from this post hoc scrutiny but the results of these methodologically reputable randomized trials cast grave doubts on the validity of orthodox claims about the hazards of smoking. These claims derive, in the main, from case-control and prospective studies of self-selected smokers, ex-smokers and nonsmokers which, by their very nature, can tell us much about association but nothing about cause. The study of Sandler et al. (1) does not even tell us about associations with passive smoking; it does, however, shed some interesting light on cancer associations with the smoking/nonsmoking status of the spouse.

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Philip R. J. Burch
Department of Medical Physics
University of Leeds
The General Infirmary
Leeds LS1 3EX, U.K.

THE AUTHORS REPLY

Friedman (1) and Mantel (2) have expressed some concerns about our passive smoking findings that are concerns for us as well (3). We agree that it would have been useful to have information on a greater number of potential confounding variables. Unfortunately, when conducting a study of many cancers, it is difficult to do justice to individual sites because risk factors vary widely by site.

While the possibility of confounding variables exists, some of those suggested by Friedman and Mantel are not likely to explain our findings. We collected information on alcohol consumption, and adjustment for alcohol intake did not alter our results. Marijuana use is also not likely to be a factor, since most of our cases were older than 40 years of age and from largely poor and rural areas. Occupational exposures may be important, although it is difficult to see how occupation of the subject would be associated with spouse's smoking, other than as an indicator of social class. Simple stratification into white and blue collar occupations did not change our results (3); and there were too few individuals with the same job for a more detailed analysis to be meaningful. Information on reproductive factors would have been useful and should certainly be included in subsequent studies given the observed associations with cancers of the breast and cervix. Since many of the factors thought to increase the risk of cervical cancer are thought to decrease the risk of breast cancer, however, it is not clear that those factors could explain our finding of elevated risk at both sites. Sexual behavior of husbands may also be important in cervical cancer risk, but reports suggest that this does not entirely explain the observed associations with spouse smoking (4, 5).

Burch points out that the smoking habits of the spouse may be a poor surrogate for passive smoke exposure (6). Certainly total passive smoke exposure will be underestimated as Friedman's data suggest (7). However, Friedman's data and others suggest that individuals who live with smokers are likely to be more exposed to other people's cigarette smoke—either because they are more tolerant of other people's smoking or because they are often exposed to other smokers when in the company of their smoking spouse (7, 8). Thus while smoking by spouse may only roughly reflect the amount of tobacco smoke exposure, it appears to distinguish the most exposed from the least exposed. Misclassification of exposure is likely to dilute any association rather than create a spurious association, unless only controls who are married to nonsmokers are also exposed at work. Furthermore, one fourth of our cases and controls (35 per cent of the females) were either housewives or unemployed, and thus likely to receive most of their smoke exposure at home. For these subjects alone, the odds ratio associated with spouse's smoking was unchanged at 1.6.

As Mantel has pointed out, past studies of cancer risk from passive smoke exposure have focused on lung cancer risk among nonsmoking women married to smokers. Our study was not designed to focus on this issue, and with only 22 lung cancers, and only two among nonsmokers, we can add little to clarify results from those studies.

While it may be surprising that strong relative risks were seen for sites not generally associated with cigarette smoking, we believe that such effects are possible. Studies indicate that passive smoking has a pervasive biologic effect (8–12), making the boundaries between "smoking related" cancer sites and other sites unclear. Some sites may be considered unrelated to cigarette smoke because risks are less dramatic than those for other sites, or because studies have not been done. While active smokers are also passive smokers, if an effect were due to some specific property of the side-

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stream smoke (e.g., increased concentration of chemicals or decreased particle size), it would be difficult to detect by comparing smokers to nonsmokers when the nonsmoking group also includes passive smokers. Alternatively, one could speculate that smokers, although at increased overall risk, may paradoxically be protected against some properties of cigarette smoke, possibly through stimulation of enzyme systems that metabolize carcinogens into less harmful compounds (13, 14). These same mechanisms may not be stimulated in nonsmokers who have different exposure to cigarette smoke.

We would not want to argue that a biologic pathway is established, but rather to say that a plausible pathway cannot be ruled out. Evidence suggests that passive smoking is not simply a lower dose of active smoking, and thus may need to be considered in a different light. Our findings are preliminary and need to be confirmed by other studies. Studies of individual cancer sites can evaluate potential confounding factors in more detail, and may be able to clarify the role of passive smoking.

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Dale P. Sandler
Richard B. Everson
Allen J. Wilcox
Epidemiology Branch
Biometry and Risk Assessment Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709

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The Relation of Passive Smoking to Lung Cancer[1]

Nancy A. Dalager,[2] Linda Williams Pickle, Thomas J. Mason, Pelayo Correa, Elizabeth Fontham, Annette Stemhagen, Patricia A. Buffler, Regina G. Ziegler, and Joseph F. Fraumeni, Jr.

Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, Maryland 20892 [N. A. D., L. W. P., T. J. M., R. G. Z., J. F. F.]; Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana 70112 [P. C., E. F.]; Division of Epidemiology and Disease Control, New Jersey State Department of Health, Trenton, New Jersey 08690 [A. S.]; and Epidemiology Research Unit, University of Texas School of Public Health, Houston, Texas 77025 [P. A. B.]

ABSTRACT

To evaluate the role of passive smoking in the development of lung cancer among nonsmokers, data were pooled from three large incident case-control interview studies. Ninety-nine lung cancer cases and 736 controls never used any form of tobacco. Overall the adjusted odds ratio for lung cancer among nonsmokers ever living with a smoker was 0.8 (95% confidence interval, 0.5–1.3) rising to 1.2 among those exposed for 40 or more years. Persons living with a spouse who smoked cigarettes were at increased risk (adjusted odds ratio, 1.5; 95% confidence interval, 0.8–2.8). When adjusted for age and gender, there was a significant trend in risk with increasing amounts smoked per week by the spouse ($P = 0.05$) and with cumulative pack-years of exposure ($P = 0.03$). This effect was limited to females, especially older women whose husbands were heavy smokers. The elevated risk associated with spouse smoking was restricted to squamous and small cell carcinomas (odds ratio, 2.9; 95% confidence interval, 0.9–9.3), which provides additional evidence linking passive smoking to lung cancer.

INTRODUCTION

The respiratory effects of passive smoking among nonsmokers are of increasing concern; evidence suggests that such exposure may increase the incidence of bronchitis and pneumonia in early life (1) and decrease lung function among nonsmoking adults (2). Recent attention has centered on the possible risk of lung cancer among nonsmokers exposed to environmental tobacco smoke (3–6), although epidemiological studies have been limited by the small number of cases available for analysis. The National Cancer Institute has recently collaborated on three large case-control interview studies of lung cancer which included questions about passive smoking. One of these studies, conducted in Louisiana, showed an increased risk of lung cancer among ever-married nonsmokers who had a spouse that smoked (6). To increase our sample size for study, data on nonsmokers from all three case-control studies were pooled and analyzed.

MATERIALS AND METHODS

Persons reporting that they had never used any tobacco products (cigarettes, pipe, cigars, snuff, or chewing tobacco) were selected from three case-control interview studies of lung cancer conducted in Louisiana, Texas, and New Jersey. The methods used in each of these studies have been reported previously (6–9). Because all three studies were designed in collaboration with the National Cancer Institute, they were similar in many respects, as shown in Table 1. Medical and pathology records were abstracted to determine the final diagnosis of each case. All were incident primary lung cancer cases diagnosed between 1976 and 1982, with nearly 100% histologically confirmed. Personal interviews were conducted with the study subject or, if the subject was deceased or too ill to respond, with a surrogate respondent. Except where noted, the questions asked in each of the study areas were very similar.

Details regarding the source and level of passive smoking exposures varied according to study area (Table 1). Texas provided the least specific data by ascertaining only if any member of the subject's household smoked while the subject was either a child or an adult and the total number of years of that exposure. New Jersey, on the other hand, inquired about the smoking habits of each household member during the subject's youth and adulthood. Louisiana requested information regarding the smoking patterns of spouse, mother, and father, but not other members of the household. An estimate of the potential underreporting of passive smoking exposure in Louisiana is provided by the New Jersey control group; 6% of the nonsmoking males reported passive smoking originating from household members other than spouse, mother, or father.

The final study population abstaining from tobacco consisted of 99 histologically confirmed lung cancer cases and 736 controls. This represented 1.2% of all male cases and 9.1% of all female cases in the original study populations, as compared to 15.0% of the male controls and 44.9% of the female controls. The final data file included all variables that could be standardized across the study areas.

Several potential confounders were examined, including gender, race, age, study area, respondent type (subject or next of kin), any self-reported chronic lung conditions, employment in suspected high-risk industries, asbestos exposure, carotene and total vitamin A intake, and whether parents had smoked. Due to the limitation imposed by small numbers, age was dichotomized into two age groups (<63 years and 63+ years). Logistic analyses utilizing three age groups did not substantially alter the adjusted odds ratios reported here. High-risk industries were those identified in a recent review of case-control studies of lung cancer (10) and included fishing, construction, lumber manufacturing, chemical and petroleum manufacturing, primary metal manufacturing, and shipbuilding. Nutrient indices were calculated from the food frequency questions for each study area, using nutrient content in a typical portion of each food (11, 12). Low intake was defined as the lowest quartile of intake for controls from each area. Because of the comparability problem resulting from the selective exclusion of persons diagnosed with chronic lung conditions in Louisiana, analyses were duplicated excluding all persons who reported having a chronic lung condition in all three study areas.

Statistical methods included the calculation of crude ORs[3] for lung cancer risks associated with passive smoking exposures. Because of the small numbers in this analysis, ORs were calculated using a 0.5 cell adjustment (13). Dose-response effects were examined using a stratified analysis and the Mantel-Haenszel test for trend (14). The logistic model was used to exclude the effects of potential confounders and to obtain maximum likelihood estimates of the adjusted ORs (15–17). Decisions concerning parameter deletions for the model were based on the t statistics for significance of the individual parameter estimates, on changes in the value of the log likelihood, and on the goodness-of-fit of the model as measured by the comparison of predicted to observed ORs, both stratified and crude. Maximum likelihood 95% CIs for the ORs were calculated from the logistic model (15) or from the stratified analysis (18).

RESULTS

The data from all three study areas were merged to examine the effect of any passive smoking exposure in the home envi-

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[2] To whom requests for reprints should be addressed, at National Cancer Institute, Landow Building, Room 3A06, Bethesda, MD 20892.

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

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Table 1 *Comparison of the three lung cancer case-control interview studies from which the nonusers of tobacco were selected*

	Study		
	Louisiana	Texas	New Jersey
Geographic area	29 Louisiana parishes	Gulf Coast of Texas	6 high-risk areas of New Jersey
Case diagnosis period	1979–1982	1976–1980	1980–1981
Study design	Hospital based	Population based	Population based
Racial groups included	Whites/blacks	Whites	Whites/blacks
Gender groups included	Males/females	Males/females	Males
Cooperation rate[a]			
Cases	91.8	91.5	87.7
Controls	93.5	87.9	73.4
No. of cases	1057 (M) 315 (F)	462 (M) 454 (F)	896 (M)
No. of controls	1073 (M) 320 (F)	451 (M) 464 (F)	1043 (M)
% histologically confirmed	97.8	100	100
Passive smoking data	Mother, father, spouse	Ever any household member	Specific household member
Nonusers of tobacco			
No. of cases	8 (M) 28 (F)	5 (M) 42 (F)	16 (M)
No. of controls	177 (M) 156 (F)	48 (M) 196 (F)	159 (M)

[a] $\frac{\text{No. of completed interviews} \times 100}{\text{No. of subjects contacted for interview}}$

ronment. There were slight variations in the passive smoking questions among the three study areas. However, since exposures from parents and spouse represented the bulk of passive smoking experienced by nonsmokers in the home, the decision to pool data on whether subjects had ever been exposed in the home environment appeared reasonable. There was no apparent increase in the risk of lung cancer among those who reported ever living with a household member who smoked (crude OR, 1.00; 95% CI, 0.64–1.56). Controlling for the strongest confounders (gender, age, and study area) reduced the OR to 0.84 (95% CI, 0.52–1.34). No significant differences were seen in the risks across sex and age strata or according to cell type of lung cancer.

A crude summary estimate of the duration of passive smoking exposure per individual was calculated for the Louisiana and New Jersey data by taking the maximum number of years that smoking was reported for mother or father and adding the years reported for spouse. In Texas, the reported value for years lived with any household member who smoked was used. In a stratified analysis, adjusted for age and gender, there was a slightly elevated OR of 1.24 (95% CI, 0.62–2.51) for those reporting 40 or more years of living with a smoker compared to 0.86 for <20 years and 0.82 for 20–39 years. These ORs were not significantly different from unity and showed no significant trend.

Since combining all known sources of passive smoking exposure might mask the effects of time period and intensity of exposure, the data were further analyzed with regard to specific sources of exposures. Because the Texas study lacked detailed data on the source and intensity of the passive smoking exposures, the remainder of the analysis was restricted to data on nonusers of tobacco from the Louisiana and New Jersey studies. The most complete information available for this combined population concerned the smoking patterns of the spouse. A total of 48 cases (22 males and 26 females) and 466 controls (318 males and 148 females) were ever-married nonusers of tobacco. The crude OR for lung cancer associated with exposure to a smoking spouse was 1.87 (95% CI, 1.03–3.42) (Table 2). Adjusting for confounding by gender, age, and study area reduced the odds ratio to 1.47. When controlling for age and gender, a significant upward trend was seen for increasing amount smoked per week by the spouse ($P = 0.05$) and cumulative pack-years of exposure ($P = 0.03$). Duration of spouse smoking, independent of amount, showed no consistent pattern.

Sex differences in risk were observed, with adjusted ORs of 1.96 for females (95% CI, 0.82–4.70) and 0.93 for males (95% CI, 0.30–2.90). This appears to reflect the greater frequency and amount smoked by the husbands of nonsmoking women compared to the wives of nonsmoking men. In the control series, women were much more likely than men to have a spouse who smoked (48.0% compared to 18.2%), and the average exposure originating from the smoking spouse was greater for women than for men (mean pack-years, 40.6 for women and 27.1 for men). The greatest risk was seen among older women (63+ years) whose husbands smoked at the highest intensity level (280+ cigarettes/week) (OR, 5.14; 95% CI, 1.40–18.95). A dose-response relationship ($P = 0.02$) occurred among females with increasing pack-years of exposure from spouse smoking, with ORs ranging up to 2.99 (95% CI, 0.96–9.37) for females with greater than 35 pack-years of exposure. The majority of nonsmoking males had 20–35 pack-years of exposure. Despite a suggestion of increased risk for men in this category (OR, 2.48; 95% CI, 0.52–10.23), the numbers were small, and no dose response was detected.

Table 2 *Odds ratios for lung cancer associated with a spouse smoking exposure among ever-married nonusers of tobacco in Louisiana and New Jersey*

Total			
Cases	Controls	Crude OR	Adjusted OR[a]
48	466	1.87 (1.03–3.42)	1.47 (0.76–2.83)
Amount spouse smoked/wk			
<140 cigarettes			1.36 (0.41–4.21)
140–279 cigarettes			1.31 (0.48–3.47)
280+ cigarettes			2.71 (0.84–8.52)
Significant trend ($P = 0.05$) for amount smoked			
Duration of spouse smoking exposure			
1–20 yr			1.73 (0.52–5.42)
21–30 yr			1.78 (0.60–5.10)
>30 yr			1.24 (0.42–3.53)
Pack-yr of exposure			
<20 pack-yr			0.78 (0.17–3.03)
20–35 pack-yr			1.90 (0.56–6.07)
>35 pack-yr			2.15 (0.84–5.40)
Significant trend ($P = 0.03$) for pack-yr of exposure			

[a] Overall OR (1.47) adjusted for gender, age, and study area in the logistic model (15–17); all other ORs adjusted for gender and age (18).

The ORs for lung cancer among nonsmokers were examined for the following histological types: adenocarcinoma; squamous and small cell carcinomas; and other cell types which included bronchioalveolar, undifferentiated, mixed, and not otherwise specified carcinomas, as well as carcinoids. As shown in Table 3, adenocarcinoma accounted for approximately one-third of the lung cancers in both sexes combined. A larger proportion

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Table 3 *Cell type distribution of lung cancer among ever-married nonusers of tobacco by sex*

Cell type	Male		Female	
	No.	%	No.	%
Adenocarcinoma	7	31.8	9	34.6
Squamous and small cell carcinoma	9	40.9	5	19.2
Other	6	27.3	12	46.2
Bronchioalveolar carcinoma	2	9.1	3	11.5
Undifferentiated	2	9.1	3	11.5
Mixed	0	0	1	3.8
Not otherwise specified carcinoma	2	9.1	3	11.5
Carcinoid	0	0	2	7.7

Table 4 *Cell type-specific ORs for lung cancer associated with spouse smoking exposure among ever-married, nonusers of tobacco in Louisiana and New Jersey*

Cell type	Total		Crude OR	Adjusted OR[a]
	Cases	Controls		
Adenocarcinoma	16	466	1.25 (0.44–3.51)	1.02 (0.33–3.16)
Squamous and small cell carcinoma	14	466	2.61 (0.93–7.32)	2.88 (0.91–9.10)
Other	18	466	2.11 (0.84–5.33)	1.31 (0.48–3.57)

[a] Logistic model included gender, age, and study area as potential confounders (15–17).

of squamous and small cell carcinomas was seen for men than for women, while other types of lung cancer were more common in women than men. The adjusted ORs (Table 4) associated with exposure to a smoking spouse varied from 1.02 for adenocarcinoma to 2.88 for squamous and small cell carcinomas.

The elevated risk for the squamous and small cell category was due mainly to the female cases in Louisiana; all five of the nonsmoking women with these cell types had spouses who smoked. The spouses of four of these five women smoked at a level greater than 25 pack-years. The men whose wives smoked showed a moderate increase in risk for squamous and small cell carcinomas (crude OR, 1.48; 95% CI, 0.34–6.39). Exclusion of all subjects who reported having a chronic lung condition did not alter the risk patterns.

Except for gender, age, and study area, no confounding was detected. The increased risks for lung cancer associated with passive smoking were not accounted for by race, respondent type, any self-reported chronic lung condition, employment in a high-risk industry, asbestos exposure, total vitamin A or carotene intake, or smoking by the parents. When the referent group was restricted to those persons reporting no passive smoking exposure from either a spouse or parent, the patterns of risk remained consistent with those we have presented.

DISCUSSION

The analysis of pooled data from three case-control studies in the United States suggested an increased risk of lung cancer among nonusers of tobacco who were married to smokers. Among women this risk appeared to be dependent on the intensity of exposure to environmental tobacco smoke as estimated by the amount smoked by their husbands. Small numbers and relatively low exposures made it difficult to assess the role of passive smoking among tobacco-abstaining men whose wives smoked. While the overall ORs were not statistically significant, the finding of a dose-dependent risk of lung cancer among nonsmoking women is consistent with other observations in the literature. Hirayama (3) in Japan and Trichopoulos *et al.* (4) in Greece reported a significant increase in the lung cancer risk of nonsmoking women whose spouses smoked. Subsequently, the prospective survey of the American Cancer Society (5) found an elevated risk for passive smoking among nonsmoking women although the excess was nonsignificant and lacked a dose-response relationship. In our study the risk of lung cancer was not increased when passive smoking exposures from childhood and adulthood were examined collectively, emphasizing the need to obtain source-specific exposure data.

When the lung cancers were analyzed by cell type, the increased risk associated with passive smoking appeared restricted to squamous and small cell carcinomas, the types most closely linked to active smoking (19). This pattern suggests that passive smoking may contribute to the risk of lung cancer through mechanisms similar to those of active smoking, although sidestream smoke contains higher concentrations of certain compounds, such as nitrosamines, compared to mainstream smoke (20). In a recent case-control study by Garfinkel *et al.* (21), significant risks for both squamous cell carcinoma and adenocarcinoma were observed among nonsmoking women exposed to a spouse smoking at home, with the risks for squamous cell cancer being 3 times greater than for adenocarcinoma. Among nonsmoking Chinese women in Hong Kong, Koo *et al.* (22) found that the risk of passive smoking was greater for squamous and small cell cancers than for adenocarcinomas.

Although our analyses included nonsmokers from three large series of lung cancer, the small number of cases still precluded any definitive answers on the carcinogenic effects of passive smoking. Other limitations concern the difficulty in quantifying exposures from passive smoking derived from interview data and in detecting relatively low-level effects. Since our study was based on questionnaires, it was not possible to evaluate certain other exposures (*e.g.*, indoor radon daughter products) that may affect the risk of lung cancer among nonsmokers.

Our study was also limited by the assessment of passive smoking exposures experienced only in the home environment and by the use of a relatively crude measure of exposure. We assumed for this analysis that the amount and duration of a spouse's smoking habit approximated the passive smoking exposure realized by an individual at home. Fuller characterization of passive smoking should address the intensity of exposure, a function of the amount of time spent in close proximity to a smoker as well as the amount that individual smokes. In our study, the sex differences observed in exposure and risk suggest the desirability of continuing to focus attention on the nonsmoking wives of smokers, while encouraging the collection of data on workplace and other nonhousehold exposures to ambient tobacco smoke.

Whenever possible, future epidemiological studies should incorporate laboratory measurements of tobacco smoke constituents and by-products such as cotinine, the major metabolite of nicotine detected in body fluids. Among nonsmokers, a dose-response relationship has been observed between the levels of urinary cotinine and self-reported exposure to passive smoking (23, 24). Thus, while the available epidemiological data on nonsmokers suggest that passive smoking increases the risk of lung cancer, mainly of the squamous and small cell types, confirmation will probably require larger study sizes as well as more extensive and innovative assessment of exposure to environmental tobacco smoke.

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Respiratory Cancer in a Scottish Industrial Community: A Retrospective Case-control Study

O.LI. LLOYD, ELEANOR IRELAND, HELEN TYRRELL and FIONA WILLIAMS
Environmental Epidemiology and Cancer Centre, Wolfson Institute of Occupational Health, Dundee

Summary

A retrospective case-control study was undertaken as part of an enquiry into possible causes of an epidemic of lung cancer in an industrial town in central Scotland. Relatives of the cases and controls answered a questionnaire which encompassed aspects of the social and occupational personal history of the deceased. Despite the length of time intervening between the period of mortality and this investigation, enough questionnaires were completed to allow the histories of the cases and controls to be usefully compared.

The results indicate that smoking and occupation contributed little to the aetiology of the outbreak of lung cancer in Armadale.

Introduction

In the small town of Armadale in central Scotland, an outbreak of primary lung cancer began in 1968 (Lloyd and Barclay, 1979; Lloyd et al., 1982). The mean standardized mortality ratio (SMR) for primary respiratory cancer from 1969–73 was the highest of all cities, burghs and landward areas in Scotland during that time (Lloyd and MacDonald, 1984). Within the town itself, many of the deaths from lung cancer formed a cluster near a source of air pollution—a steel foundry (Lloyd, 1978a, 1981). This cluster was statistically significant, with an SMR, based on Scottish rates, of 206 between 1968 and 1977. The cases of primary lung cancer had been identified initially by examining the diagnoses on the death certificates of the local parishes in the Registrar General's Office for Scotland. The validity of most of those diagnoses was confirmed later by obtaining supporting information from other sources of diagnostic data (Tyrrell and Lloyd, 1983).

During the earlier stages of the enquiry, the occupational and social backgrounds of the deceased were investigated on a preliminary basis, through the use of hospital case notes, death certificates and discussions with local doctors. No unusual features were identified which would have explained so many cases of lung cancer in such a short period (Lloyd, 1978b; Lloyd et al., 1982). Nevertheless, to test the hypothesis that the cluster of lung cancer might be causally linked to occupation and smoking habits, it was considered essential to undertake more detailed enquiries into the social and occupational backgrounds of the deceased. We decided to construct a questionnaire which would be answered by relatives of the deceased in the form of a retrospective case-control study. Most of the questions concerned details of the smoking habits and occupational experiences of the deceased with additional questions covering personal and familial histories of related lung disease and cancer, and the residential histories.

Methods

The period covered by the study was 1968–74, when the SMR for the town had been found high. The cases were residents of Armadale who had died during 1968–74 with the diagnosis of primary lung cancer on the death certificate. The controls were chosen from a list of residents of Armadale who had died from any cause other than lung cancer, during the same period. Preliminary work had shown that this width of diagnostic frame was necessary to allow matching for the social characteristics in this small population. The cases were computer-matched consecutively for sex, age at death ± 10 years, year of death ± 5 years, and by social class I–V. Anticipating the problem of failure to trace some controls, reserve controls were obtained for as many cases as was possible.

Ethical permission was obtained at district and area health board levels for tracing and interviewing next-of-kin or other relatives (hereafter referred to collectively as relatives). The agreement of the local family doctors was also obtained.

Using the experience gained from a pilot study of a similar questionnaire within an occupational workforce elsewhere, a final questionnaire was constructed. Since the major areas of interest were the tobacco habit and occupational history of the deceased, most of the questions covered details of those areas. For smoking history, questions included the average, minimum and maximum numbers of cigarettes smoked daily, the age of starting smoking, the number of years of that habit, the use of pipes and cigars and filter cigarettes, the brand name of the tobacco used (from which the tar content was estimated), the inhalation practice, the habit of smoking at work, and exposure to passive smoking at work and at home. There was also a question on the certainty with which this information was given. For occupational history, questions covered occupations since leaving school, and exposure to specified chemical and physical factors; details were requested of any time spent at particular types of work within the coalmining and steel foundry industries. For the previous medical history of the deceased, questions covered experience of non-malignant respiratory diseases. For the familial medical history, the questions also included cancers and coronary heart disease. The questions on place of residence covered addresses since 1940. These addresses were subsequently assigned to Zones A–E, (*see Fig.* 1), which were aggregates of enumeration districts of the town at the 1971 census and which had been used previously in epidemiological investigations.

Questions also covered residential proximity to industrial sources of environmental air pollution, and the degree to which that pollution inconvenienced the individual concerned. The type of fuel used normally for

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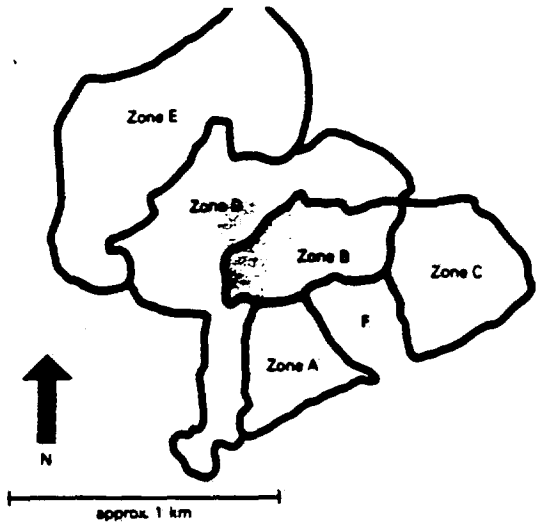

Fig. 1. Zone map of Armadale. Zone A: west of foundry; Zone B: north of foundry; Zone C: east of foundry; Zone D: intermediate; Zone E: distant; F: foundry.

heating and cooking was investigated. Finally, various combinations of factors were examined to try to identify signs of interaction between them in promoting the elevated mortality from lung cancer.

The questionnaire was administered to the nearest surviving relative of the deceased, by one of two interviewers. To avoid interviewer bias, the interviewers were not told whether the person they were interviewing was a relative of a case or of a control. The relatives were traced mainly with the assistance of the local general practitioners and other staff at the only group practice in the town. Where they were unable to identify surviving relatives still living in the area, they were often able to supply names and addresses of friends who knew where the relatives could be found. Other sources used for tracing relatives were a local minister, and, for some of the more unusual names, the local telephone directory.

For those cases and controls whose relatives could not be contacted, other sources of information were used to ascertain only the location of the last known address.

The information derived from the questionnaire was subjected to frequency analysis; and for many exposures, the relative risks and their 95 per cent confidence limits were used to test the null hypothesis that the answers of the cases and controls did not significantly differ from each other.

Results

General

The interviews were carried out between November 1982 and March 1984.

Table I. Age at death of cases and controls

	Age group					
	30–39	40–49	50–59	60–69	70–79	80+
Cases	2 (5%)	1 (2%)	4 (10%)	15 (36%)	14 (33%)	6 (14%)
Controls	0 (0%)	2 (5%)	6 (14%)	15 (36%)	15 (36%)	4 (10%)

Of a possible 137 relatives on the list of interviewees, 103 (75 per cent) were traced and interviewed. Nineteen controls were subsequently eliminated: either they were the 'reserve' controls of cases for which a matched control had already been obtained, or the cases to which they were matched had no known relatives—the relatives having migrated to an unknown location or abroad. The final total of interviews used for the analysis of the data was 84: 42 cases, each with one matched control.

Of the 42 cases of primary lung cancer obtained for the analysis, 35 were males. The age at death of the cases ranged from 37 to 86 years; those of the controls were from 47 to 84 (*Table I*). Because the lapse of time between the year of death and this study taking place was up to 18 years, it was found that many of the spouses of the cases and controls had died. Hence the largest group of informants was the daughter/son group, the second largest being the husband/wife group (*Table II*). Thus, information about 30 of the cases and 32 of the controls was obtained from a close relative (spouse, sibling, son or daughter).

Smoking History

There were no statistically significant differences between the answers of the cases and controls in any of the questions (*Table III*).

More cases than controls were found for those who had ever smoked, for cigarettes only, cigar/pipe smokers and for smokers of plain cigarettes; for small and large numbers of cigarettes smoked, for high tar content of cigarettes; and for inhaling practice.

More controls than cases were found for non-smokers and smokers of filter cigarettes; for medium (15–29) consumption of cigarettes; for being permitted to smoke at work; and for passive smoking both at work and at home.

The cases started smoking at an earlier age (18·7 years) and continued the habit for longer (45·6 years).

There was less certainty about the smoking habits of the controls than about the habits of the cases.

Occupational history

The differences between the number of cases and controls employed in the major industries of the town (coal mines, steel foundry, brickworks), were not statistically significant (*Table IV*). Slightly more cases than controls

Table II. Relationship between respondent and deceased

	Husband/ wife	*Son/ daughter*	*Brother/ sister*	*Nephew/ niece*	*Grandchild*	*In-laws*	*Other*
Cases	13 (31%)	13 (31%)	4 (10%)	7 (17%)	1 (2%)	3 (7%)	1 (2%)
Controls	8 (19%)	17 (41%)	7 (17%)	7 (17%)	1 (2%)	2 (5%)	0 (0%)

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Table III. Characteristics of the smoking history of cases and controls

Category	*Characteristic*		*Cases*	*Controls*	*Relative risk**	*95% confidence limits*
	Never smoked		3	8	1·0	
	Cigarettes only		28	26	2·87	0·68–11·94
	Cigarettes and pipe or cigar		4	4	2·67	0·39–18·16
	Pipe or cigar only		7	4	4·67	0·76–28·47
Ever Smoked: cigarette/pipe/cigar	Smokers		39	34	3·06	0·75–12·44
	Filter cigarettes		6	8	1·0	
	Plain cigarettes		19	12	2·11	0·59–7·61
	Plain and filter		5	4	1·66	0·31–9·01
Mean quantity smoked for duration of habit	1–14 Cigarettes/day		11	7	1·0	
	15–29 Cigarettes/day		10	13	0·49	0·14–1·73
	30+ Cigarettes/day		9	8	0·72	0·19–2·78
Tar content (estimated from brand name)	Low-medium tar		5	7	1·0	
	High tar		21	14	2·1	0·55–7·95
Includes cigar/pipe smokers	Inhaling practice					
		Yes	26	24		
		No	3	6		
	Permitted to smoke at work					
		Yes	10	13		
		No	25	19		
Continual exposure to passive smoking	At work	Yes	10	15	0·56	0·21–1·50
		No	25	21	1·0	
	At home	Yes	32	34	0·84	0·29–2·45
		No	9	8	1·0	
(in years)	Age started smoking		$\bar{x}$ 18·7	19·2		
			SD 9·1	8·9		
(in years)	Duration of habit		$\bar{x}$ 45·6	43·7		
			SD12·7	12·2		
Reliability of information	Very reliable		3	3		
	Fairly reliable		22	14		
	Some idea		6	7		
	Uncertain		3	4		
	Guess		3	2		

* Relative risk = 1·0 identifies baseline category.

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had worked in the coal mines at some time, but fewer had worked in the local steel foundry. Almost equal numbers of cases and controls had worked in the local brickworks. All other occupational groups contained negligible numbers of both cases and controls. Some individuals had worked in more than one industry.

When coal mining and foundry work were categorized according to subgroups of occupation, the biggest difference between cases and controls was for the moulder/coremaker group of foundry workers, with 1 case and 5 controls. For exposure to chemical agents, there were no significant differences between cases and controls.

Personal and familial medical histories

Considerably more cases than controls were reported to have had a history of bronchitis (*Table V*). This difference was statistically significant, with a relative risk of 3·71 and 95 per cent confidence limits of 1·19–11·58.

Due to the difficulties with recall experienced by the relatives, it was not possible to obtain a reliable or comprehensive history of chest disease or of all types of cancer in the families of cases and controls. However, in the data available there were no significant differences between the numbers of relatives of cases and controls for the histories of asthma, lung tuberculosis, and all cancers.

Only slight differences between cases and controls were noted for the types of fuel used for domestic cooking and heating (*Table VI*).

Residential history

Most of the cases and controls had been lifelong residents of Armadale; only 5 cases and 8 controls had ever lived outside the town. Of those who had resided outside Scotland, 4 were cases (2 in the USA, 1 in Australia, 1 in Newfoundland) and 6 were controls (3 in England, 1 in the USA, 1 in France, 1 in Poland).

The modal number of addresses for each person was 2; 16 cases and 17 controls had that number. No person had lived in more than 4 addresses.

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include persons who ever worked in the industry)

Category	Characteristic		Cases	Controls	Relative risk*	95% confidence limits
Working history	Other occupations		17	24	1·0	
	Coal mining		21	17	1·74	0·71–4·25
	Steel foundry		9	13	0·98	0·34–2·82
	Brickworks		6	7	1·21	0·35–4·26
Exposure to	Coal dust	Yes	20	15	1·78	0·69–4·60
		No	15	20	1·0	
	Sand, silica, cotton or mineral fibres	Yes	4	4	1·0	
		No	31	31	1·0	
	Metal dust/ fumes	Yes	7	7	1·0	
		No	28	28	1·0	
	Direct and intense heat	Yes	2	2	1·0	
		No	33	33	1·0	
Mine workers only	Surface and/or general		5	4	1·0	
	Faceworker		13	11	0·95	0·20–4·44
	Surface and face-worker		3	2	1·2	0·13–10·99
Foundry workers only	Moulder/coremaker		1	5		
	Furnaceman		1	0		
	Sandblaster		2	0		
	Smith/forger		0	1		
	Specific occupation unknown		4	1		

* Relative risk = 1·0 identifies baseline category.

Table V. Characteristics of the medical history of cases and controls

Category	Characteristic		Cases	Controls	Relative Risk*	95% confidence limits
Personal medical history	Bronchitis	Yes	14	5	3·71	1·19–11·58
		No	27	35	1·0	
	Pneumonia	Yes	6	5	1·21	0·34–1·47
		No	35	35	1·0	
	Pneumoconiosis	Yes	10	7	1·52	0·52–4·49
		No	31	33	1·0	
	Unspecified respiratory	Yes	25	21	1·41	0·58–3·40
		No	16	19	1·0	
Family medical history	Coronary heart disease		11	17	1·0	
	Asthma		1	3	0·51	0·05–5·56
	T.B.		2	0		
	Lung cancer		2	3	1·03	0·15–7·19
	Other cancers		8	3	4·12	0·89–18·88
	Pneumoconiosis		4	8	0·64	0·16–2·61

* Relative risk = 1·0 indentifies baseline category.

Within Armadale, there were no statistically significant differences between numbers of cases and controls who had ever lived in the various zones (*Fig.* 1). More cases than controls had ever lived in Zone A, the area with the cluster of lung cancer deaths (*Table VII*). When the period 1965–74, (i.e. just before and during the time when the SMRs for lung cancer were abnormally high) was examined as a separate unit, the difference between the numbers of cases (12) and controls (8) who had lived in Zone A was even greater (*Table VIII*). The only other zone where the cases exceeded controls was Zone C, directly east of the foundry (*Fig.* 1); during the period 1965–74, 6 cases and 3 controls had lived there.

Table VI. Type of fuel or power used for domestic heating and cooking

	Gas	Coal	Electric	Coal and other
Heating				
Cases	2 (5%)	35 (83%)	1 (2%)	4 (10%)
Controls	1 (2%)	35 (83%)	3 (7%)	3 (7%)
Cooking				
Cases	32 (76%)	6 (14%)	2 (5%)	1 (2%)
Controls	33 (77%)	4 (10%)	3 (7%)	2 (5%)

Fifteen lung cancer cases had no known relatives and were therefore *not* included in the 42 cases in this study.

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Table VII. Ever lived in each zone

	Zones				
	A	B	C	D	E
Cases	14	11	7	17	7
Controls	11	12	4	21	7

Table VIII. Dates of residence in zones A and C

	1940–64	*1965–69*	*1970–74*
Zone A			
Cases	2	11	1
Controls	3	7	1
Zone C			
Cases	0	3	3
Controls	1	1	2

Table IX. Location of last known address of cases and controls whose relatives could not be contacted

	A	*B*	*C*	*D*	*E*
Cases	3	3	1	6	2
Controls	8	6	2	9	5

However, they were matched to 30 controls (some other cases having a reserve control). When their last known addresses were plotted by zone, there were no significant differences in distribution between cases over controls (*Table IX*). Thus there was no bias in the geographical distribution of the cases included in the study.

Of those who were conscious of a neighbouring source of environmental air pollution, the only major difference between numbers of cases and controls was for the combination of steel foundry and brickworks (*Table X*). But the cases did not complain of resulting inconvenience much more than did the controls.

Various combinations of factors, including residence in Zone A were analysed (*Table XI*), but no significant signs of interaction were found which might have contributed strongly to the elevated mortality from lung cancer. The combination of residence in Zone A during 1965–74 and a history of bronchitis showed the greatest difference. A similar difference was found for the combination of heavy smoking (more than 29 cigarettes daily and middle-to-high tar content) and a history of bronchitis. In all comparisons, however, the numbers were too small to allow a reasonable opportunity of finding statistical significance.

Discussion

Despite the long time between the increased incidence of lung cancer and the interviews with the relatives, the

Table X. Proximity to pollution source

Comment	*Variable*	*Cases*	*Controls*	*Relative risk**	*95% confidence limits*
Applies only when residence was within ½ mile of the industry	Steel foundry only	11	11		
	Gas works and foundry	1	1		
	Brickworks, gas and foundry	1	4	0·50	0·01–27·11
	Brickworks, foundry	20	13	3·08	0·86–11·07
	Steelworks, brickworks and coal mine	4	3	2·67	0·42–16·83
Outwith ½ mile proximity		5	10	1·0	
Awareness of atmospheric pollution	Yes	15	12		
	No	27	30		

* Relative risk = 1·0 identifies baseline category.

Table XI. Combinations of factors (3-way tables)

Factors:—
1. Resident in zone A between 1965–74
2. Heavy smoker, i.e. over 29 per day, and middle or high tar
3. Ever worked as miner
4. Ever worked in foundry
5. History of bronchitis

	Cases	*Controls*
① and ②	2	3
① and ③	4	3
① and ④	5	4
① and ⑤	4	0
② and ③	6	6
② and ④	3	2
② and ⑤	6	2
③ and ④ and ①	0	0
③ and ④ and ②	3	0

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view allowed a comprehensive picture to be gained of the occupational and social backgrounds of cases and controls. This experience was similar to that reported in an investigation of asbestos-related mesothelioma (Finlayson et al., 1971).

In general the occupational experiences of both cases and controls were very similar. Some epidemiological studies have suggested that workers in ferrous industries are at a greater risk of dying from lung cancer than persons in the general population; the risk of lung cancer has been related especially to exposure to 'hot metal', with moulders particularly at risk (Morrison, 1957; Hueper, 1966; Radford et al., 1976; OPCS, 1978; Wall, 1980). However, this present study confirmed the results of preliminary work (Lloyd et al., 1982) in finding no evidence to support the association of lung cancer with foundry work in general; nor was an association found with hot metal exposure or with moulding in particular. There were no reports of asbestos or radon exposure. No statistically significant differences were found between the numbers of cases and controls exposed to coal, dust, sand, silica, direct and intense heat from industrial furnace, metal dusts, or fumes from petroleum and its products. Hence, occupational experiences did not appear to have contributed in any important way to the elevated mortality from lung cancer in Armadale. (The similarity between the numbers of cases and controls having a coal mining history and an exposure to coal dust indicated the reliability of the respondents' answers, at least in that context of occupational experience.)

Because the most important cause of lung cancer is known to be cigarette smoking, the questions about smoking habits were very detailed. However, since this study relied on individuals remembering what their relatives were doing up to 15 years previously, we could not obtain as full and comprehensive an account of the smoking habits of the deceased as could be expected in more favourable circumstances. For instance, while it was fairly easy to obtain a figure for the amount of tobacco smoked daily, the respondents found it far more difficult to provide information concerning inhaling practice, and often had difficulty with brand names. However, an examination of the information about the amount, the duration of habit, the types of cigarette smoked, the opportunity to smoke at work, and about passive smoking, showed no significant differences between cases and controls in any factor. For some risk factors, there was an excess of controls. The biggest difference between the groups (19 cases and 12 controls having smoked plain cigarettes) could have been a consequence of the greater amount of missing and uncertain information found with the control group.

When considering familial medical histories it was noted that a history of lung cancer in the close family was as infrequent amongst the cases as amongst the controls. A family history of all other cancers was more frequent with the cases than with controls, but the small numbers in both groups make this finding difficult to interpret.

The high frequency of a history of bronchitis amongst the cases, which was the only statistically significant difference between cases and controls, is consistent with evidence that bronchitis and lung cancer are both associated with air pollution, as well as with cigarette smoking.

Indoor air pollution from cooking and heating appliances has been suspected as a pathogenic factor for respiratory disease (Florey et al., 1979; Lende, 1980). No significant difference in the use of such appliances by cases and controls was apparent in this study. The relatively small difference between numbers of cases and controls who had ever lived in Zone A, an area which was subject to relatively high air pollution (Yule and Lloyd, 1984; Gailey and Lloyd, 1983, 1985) and where an excess of lung cancer had been discovered (Lloyd, 1978a), might have resulted from our inability to eliminate from our controls all those whose deaths could have been linked with the air pollution through causes other than lung cancer. However, because of the small size of the town and hence the small number of deaths each year, deaths from all other causes had to be included as potential controls in order to allow the other characteristics of the cases to be matched. Nevertheless, despite this difficulty in the design of the study, the findings were consistent with the statistically significant excess of cases observed previously in an area close to the site of a polluting industry (Lloyd et al., 1982; Lloyd, 1982).

In summary, this study demonstrated that social and occupational factors were probably not of importance in the outbreak of lung cancer in Armadale during 1968–74. Hence the hypothesis that environmental air pollution might have played a significant aetiological role was not invalidated. The study also illustrated the practicability of undertaking a retrospective study covering a wide range of occupational and social factors by means of questionnaires given to relatives of people who had died up to 15 years before the start of the study.

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Requests for reprints should be addressed to: Dr O. Ll. Lloyd, Environmental Epidemiology and Cancer Centre, Wolfson Institute of Occupational Health, Department of Community Medicine, Level 5, Medical School, Ninewells, Dundee.

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EFFECT OF PASSIVE SMOKING IN LUNG CANCER DEVELOPMENT IN WOMEN IN THE NARA REGION

By H. Katada, R. Mikami, M. Konishi, Y. Koyama, and N. Narita

Second Department of Internal Medicine,
Nara Prefectural Medical University

Translation from Japanese

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EFFECT OF PASSIVE SMOKING IN LUNG CANCER DEVELOPMENT IN WOMEN IN THE NARA REGION

Hitoshi Katada, Riichiro Mikami, Mitsuru Konishi, Yasuhiro Koyama and Nobuhiro Narita

Second Department of Internal Medicine, Nara Prefectural Medical University

Introduction

It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis has become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women.

1. Subjects and Method

1) Subjects

The subjects were 25 women with lung cancer who were admitted to our department. They averaged 67.5±8.8 years of age. Based on histology there were 7 cases of squamous cell carcinoma, 5 of small cell carcinoma and 13 of adenocarcinoma. The age averages for the above groups were 71.4±7.8, 66.2±9.3 and 65.8±9.0 years, respectively. As controls, 50 cases of non-malignant hospitalized patients matched for sex and age (within 2 years) were selected. Their age average was 67.6±8.5 years.

2) Items of examination

To gather data on active and passive smoking (current and past) and familial accumulation of cancer, detailed questioning was conducted regarding personal history, concomitant disease, exposure to atmospheric pollution, stress, occupation, obesity, alcohol consumption and other items with the patient herself and with the family. Passive smoking was defined as exposure to smoking more or less daily through living with a smoker, and the amount was defined as the number of cigarettes smoked by the smoker each day multiplied by the number of years of exposure. Familial accumulation was based on occurrence or absence of malignancy in relatives to the 3d degree. Comparison with controls was made on the basis of significance of difference and relative risk regarding smoking and familial factors for each histologic type of tumor. Squamous cell carcinoma and small cell carcinoma which are regarded as

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having an intimate relation to smoking were grouped together.

2. Results

1) Squamous cell carcinoma (Table 1)

There were 4 patients who were active smokers out of 7. Passive smoking was experienced in all, but 6 were currently exposed while 5 had a history of exposure. Three reported exposure at an early age. Familial accumulation was observed in 4 cases, of which 3 were lung cancer, a high incidence, while 2 were gastric cancer. General history included one case of ovariectomy and 2 cases of ulcer of the digestive tract. Four had experienced atmospheric pollution and 3 reported stress. In the 3 non-smokers (cases 5, 6 and 7), passive smoking and familial cancer both occurred. These patients were the most elderly.

2) Small cell carcinoma (Table 1)

Four of 5 were active smokers. Passive smoking occurred in all 5, these all being exposed currently, while one case had a history of passive smoking and one could not be determined regarding this information. Familial accumulation was found in 4 cases, 3 being cases of gastric cancer, a high incidence. As for personal history, there was one case each of uterine cancer and hysterectomy and one case of breast cancer. Exposure to atmospheric pollution occurred in 2 and stress in 4. In the one non-smoker (case 5) there was intense passive smoking. The individual had a history of surgery for breast cancer, and her two younger sisters had had breast cancer and uterine cancer (individually). This group of patients averaged 5 years younger than the cases of squamous cell carcinoma.

3) Adenocarcinoma (Table 2)

There was not a single active smoker out of 13, but all had been exposed to passive smoking, 12 out of 13 being currently exposed. There were 10 out of 11 who had a history of passive smoking, 8 since early childhood. Familial incidence of cancer was present in 11 out of 13, two being lung cancer, 7 gastric cancer, 4 esophageal cancer and 2 colon cancer. Three had uterine fibroid and 1 had undergone hysterectomy. There were 2 cases of respiratory disease. Exposure to atmospheric pollution occurred in 5, and stress in 4. In 11 out of 13 there was passive smoking along with familial cancer. In the other two there was intense passive smoking in one and passive smoking plus pulmonary tuberculosis in the other.

4) Controlled studies (Tables 3, 4 and 5)

Regarding passive smoking (Table 3), there was a significant difference between lung cancer cases and controls in the amount of exposure ($p<0.05$), although no definite difference could be observed according to tumor cell type. When the cases were grouped into those who had been exposed up to the present time, those who had been exposed in the past and those who had been exposed since early childhood,

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Table 1. Squamous cell carcinoma and small cell carcinoma of the lung in women.

A. Squamous cell carcinoma.

	Age	Active smoking	Passive smoking		Familial cancer	Personal history of disease	Concomi-tant illness	Air pol-lution	Occu-pation	Stress	Others
			Past	Present							
1. T.O.	78	500	son + husb 1,600 cigs	father, loose tob	—	pyelitis	hyper-tension	+	house-wife	—	husband: gastric ca. TB
2. M.R.	57	853	husb 1,653 son 400 cigs	younger bro. loose tob	—	excision of ovary	—	—	house-wife	—	
3. N.O.	70	330	husb 400 cigs	—	Aunt (LC)	Gastric ulcer	Lumbar deforma.	—	house-wife	—	
4. K.S.	70	300	—	father loose tob husb 360 cigs	—	Lumbar herniat.	Hyper-tension	—	house-wife	+	
5. T.N.	68	—	husb 960 cigs	father 400 cigs	older bro(LC) Yng(LC) sister	Injury rt. hand	—	+	plastic industry	—	
6. T.S.	79	—	husb +	—	Mother (GC) old (LC) bro.	duodenal ulcer	Neuro-genic cystitis	+	house-wife	+	
7. K.N.	78	—	son 1,600 cigs	husb 450 cigs	father (GC)	appendic. hypo-tension	Parkins. angina pectoris	+	pawn-broker	+	

N.S.

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Table 1. (con't) B. Small cell carcinoma (women)

	Age	Active smoking	Passive smoking: Past	Passive smoking: Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. K.Y.	67	350	son 100 cigs	—	mother (GC), old sister (RC)	uterus ca, hepatic gall stone	cardiac insuff.	—	housewife	+	
2. E.Y.	50	625	husb +	—	father (GC)	hysterec. gast.uld lymph node TB	—	+	family factory	+	
3. T.H.	70	500	husb + daught +	—	old bro (GC), yng bro (?C)	gall stone cere. embol	—	—	housewife	+	
4. F.M.	72	300	husb 370 cigs, son 600 cigs	?	—	pul TB, bronch. asthma	—	+	housewife	—	
5. T.T.	72	—	daughter cig 120, grand child cigs 550	fath. 320, uncle 300, husb 640 cigs	yng sis (MC), yng sis (UC)	breast ca	—	—	teacher	+	divorced

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Table 2. Adenocarcinoma in women

A. Adenocarcinoma

	Age	Active smoking	Passive smoking: Past	Passive smoking: Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. K.Y.	73	—	son +	mother pipe husb 200 cigs	old sister (LC)	pleurisy	hyper-tension	+	camera store	—	
2. Y.M.	75	—	husb 1,040 cigs son +	?	old bro (EC)	traffic accident	—	—	agri-cult.	—	
3. Y.M.	66	—	husb 700 cigs	father +	mother (CC)	uterine fibroid	hyper-tension atr. fibril.	—	house-wife	+	depression
4. T.M.	77	—	son 1,050 cigs	father + husb 125 cigs	old sis (GC)	—	hyper-tension	—	house-wife	—	
5. K.M.	71	—	husb 470 cigs	father- mother pipe mother- pipe	(GC) old bro (LC)	hysterec. herpes	—	—	agri-cult.	—	
6. Y.T.	76	—	son 310 cigs	father + grand 300 parent	fath (RC) moth (GC)	fracture of vertebra	hyper-tension	—	agri-cult.	—	
7. S.W.	66	—	son 400 cigs	—	mother (EC) old brother (GC)	wrist fracture	—	furnace (soot)	fish market	±	
8. Y.F.	50	—	—	father 150 husb 200 cigs	grand-fath (EC) aunt (GC)	uterine fibroid hernia	—	—	house-wife	—	
9. T.M.	60	—	husb 600 son 180 cigs	?	uncle (GC) aunt (LyC) MLy) child	—	rheuma-tism	—	house-wife	+	
10. H.O.	49	—	+ at work	husb 480 cigs	cousin (GC) cousin (?C)	—	—	+	coffee shop	+	
11. H.Y.	64	—	husb 700 cigs	father mother pipe	(EC)	uterine fibroid lung absc.	—	+	house-wife	—	2 —
12. S.S.	68	—	son 580 son 100 cigs	husb 800 uncle 200 yng 180 bro cigs	—	—	hyper-tension	—	agri-cult.	—	husband: lung ca
13. T.I.	61	—	husb 800 cigs	fath 600 cigs	—	—	pulmonary TB	+	agri-cult.	—	pul (+) infection

ALL N.S.

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the greatest influence was found to be that of present exposure, with a significant ($p < 0.05$) difference from the controls. Some differences were also seen in cases of all lung cancers and of adenocarcinoma who had history of passive smoking.

Among active smokers (Table 4), there was no difference between the lung cancer group and controls, but the combined number of cases of squamous cell carcinoma and small cell carcinoma was significantly ($p < 0.01$) higher in active smokers compared with non-active smokers, while the incidence of adenocarcinoma actually had a negative correlation with active smoking.

Among passive smokers (Table 4), when compared 1:1 with controls who were also non-active smokers, no significance was observed in the history of exposure, overall, present or past, but the ratio was virtually the same as that when active smokers were included (Table 3). Some difference, however, were observed for overall lung cancer and adenocarcinoma cases with history of past exposure to smoking.

When cumulative family incidence of cancer (Table 5) was investigated, it was found to create a significant ($p < 0.001$) difference between lung cancer cases and controls, the association being especially strong with adenocarcinoma, indicating that family incidence of cancer was an important factor in this type of cancer.

When smoking and familial cancer were combined (Table 5), the results were not significant with active smoking, but significant with passive smoking. The increase in risk when familial cancer and passive smoking were combined over that of familial history alone was as follows: All lung cancers + present exposure to passive smoking, x11.7; all lung cancers + past exposure to passive smoking, x 10.0; all lung cancers + active or passive smoking, x17.3; squamous cell carcinoma + small cell carcinoma + present exposure to passive smoking, x7.0; squamous cell carcinoma + small cell carcinoma + active or passive smoking, x40.8; and adenocarcinoma + past exposure to passive smoking, x26.7.

3. Discussion

The question of lung cancer development in non-smokers exposed over extended periods to smoking by others in the family and at the place of work has become a social concern not only in the United States but also in Japan.

In the present study, we gathered detailed information on the history of illness and family background in 25 cases of lung cancer in women, and investigated the relations among passive smoking, active smoking and familial incidence of cancer. The subjects were residents of Nara Prefecture, most of them housewives or women engaged in farming. The passive smokers in this study were all living with one or more smokers, therefore presumably exposed to passive smoking daily from at least

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	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Passive smoking (Total)	$\frac{23}{23}$ (100)			$\frac{36}{45}$ (80)	<0.05	13.2
		$\frac{12}{12}$ (100)		$\frac{17}{24}$ (71)	<0.1	10.7
			$\frac{13}{13}$ (100)	$\frac{23}{26}$ (88)	NS	—
Passive smoking (At present)	$\frac{23}{25}$ (92)			$\frac{32}{50}$ (64)	<0.05	6.5
		$\frac{11}{12}$ (92)		$\frac{14}{24}$ (58)	<0.1	7.9
			$\frac{12}{13}$ (91)	$\frac{18}{26}$ (69)	<0.1	5.3
Passive smoking (In the past)	$\frac{16}{22}$ (73)			$\frac{20}{44}$ (45)	<0.1	3.2
		$\frac{6}{11}$ (55)		$\frac{9}{22}$ (41)	NS	—
			$\frac{10}{11}$ (91)	$\frac{11}{22}$ (50)	<0.1	10.0
Passive smoking (In childhood)	$\frac{13}{22}$ (59)			$\frac{20}{44}$ (45)	NS	—
		$\frac{4}{11}$ (36)		$\frac{9}{22}$ (41)	NS	—
			$\frac{8}{11}$ (73)	$\frac{11}{22}$ (50)	NS	—

( ): %, NS: not significant

Table 3. Passive smoking and lung cancer in women (controlled study 1).

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	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Active smoking (+)	$\frac{8}{25}$ (32)			$\frac{14}{50}$ (28)	NS	—
		$\frac{8}{12}$ (67)		$\frac{4}{24}$ (17)	<0.01	10.0
			$\frac{0}{13}$ (0)	$\frac{10}{26}$ (38)	<0.05	0.06
Passive smoking (at present)	$\frac{17}{17}$ (100)			$\frac{14}{17}$ (82)	NS	—
		$\frac{4}{4}$ (100)		$\frac{3}{4}$ (75)	NS	—
			$\frac{13}{13}$ (100)	$\frac{11}{13}$ (85)	NS	—
Passive smoking (in the past)	$\frac{16}{17}$ (94)			$\frac{17}{17}$ (71)	NS	—
		$\frac{4}{4}$ (100)		$\frac{3}{4}$ (75)	NS	—
			$\frac{12}{13}$ (92)	$\frac{9}{13}$ (69)	NS	—
Passive smoking (in child-hood)	$\frac{13}{15}$ (87)			$\frac{7}{15}$ (47)	<0.1	7.4
		$\frac{3}{4}$ (75)		$\frac{2}{4}$ (50)	NS	—
			$\frac{10}{11}$ (91)	$\frac{5}{11}$ (45)	<0.1	12.0

( ): %, NS: not significant

Table 4. Passive smoking and lung cancer in women (controlled study 2).

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	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Cumulative familial cancer	18/25 (72)			13/50 (26)	<0.001	7.3
		7/12 (58)		7/24 (29)	NS	—
			11/13 (85)	6/26 (23)	<0.001	18.3
Active smoking + familial cancer	4/25 (16)			4/50 (8)	NS	—
		4/12 (33)		2/24 (8)	NS	—
			0/13 (0)	2/26 (8)	NS	—
Passive smoking (at present) + familial cancer	18/25 (72)			9/50 (18)	<0.0001	11.7
		7/12 (58)		4/24 (17)	<0.05	7.0
			10/13 (77)	5/26 (19)	<0.001	14.0
Passive smoking (in the past) + familial cancer	11/22 (50)			4/44 (9)	<0.001	10.1
		3/11 (27)		2/22 (9)	NS	—
			8/11 (73)	2/22 (9)	<0.001	26.7
Active or passive smoking + familial cancer	23/25 (92)			20/50 (40)	<0.001	17.3
		12/12 (100)		9/24 (38)	<0.005	40.8
			11/13 (85)	11/26 (42)	<0.05	7.5

( ): %, NS: not significant

Table 5. Familial incidence of cancer and smoking in relationship to lung cancer in women (Controlled study 3).

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the evening until the following morning.

It was found that present exposure to passive smoking was more influential than past exposure; that active smoking had a fairly marked effect on the development of squamous cell carcinoma or small cell carcinoma; and that in these histologic types, current (up to the present time) exposure to passive smoking had a marked effect. On the other hand, there was virtually no effect of active smoking on the development of adenocarcinoma,but there was suspicion of the effect of past or present exposure to smoking in this type of tumor.

The effect of passive smoking should be considered qualitatively and quantitatively. In assessing the qualitative effect of passive smoking, the following items should be considered: The amount of carcinogenic material in secondary smoke is greater than in the primary smoke[1]; when ten cigarettes are smoked in 1 hour, the level of COHb in the blood of the non-smoker rises to about the same concentration as that following the active smoking of one cigarette[2]; the amount of urinary nicotine of a non-smoker increases in parallel to the number of active smokers generating smoke, demonstrating a dose response effect[3];benzpyrene in the urine of a non-smoker exposed to smoke becomes detectable, and this amount decreases when the non-smoker avoids exposure to smoke[4]; upon exposure to smoking for 6 hours, the amount of mutagens in the urine of a non-smoker increases markedly[5]; and that mice and dogs exposed to smoke develop lung tumors[6]. These results suggest the possibility of lung carcinogenesis through passive smoking.

Quantitative assessment of passive smoking has been presented in the following findings: The increase in incidence of lung cancer in non-smoking wives of heavy cigarette smokers over that in non-smoking wives of non-smokers was x2.08 in Japan (Hirayama)[7], x3.4 in Greece (Trichopoulos)[9], x3.11 in the United States (Correa)[10], x1.94, also in the United States (Miller)[11], x12.78 in Kanagawa Prefecture (Inoue)[22] and x1.5-2.1 in Hiroshima and Nagasaki (Akiba)[23]. When the findings by Garfinkel (U.S.)[8] and Koo (Hong Kong)[17] are excluded, mortality of non-smoking wives from lung cancer seems to increase about two-fold. Increase in the risk of passive smoking in the family is especially marked in non-smoking women under 50 years of age, while habitual smokers are subject to both active and passive smoking[12]. Akiba[23] found that of women who are not exposed to either active or passive smoking, 100% develop either adenocarcinoma or large cell carcinoma; that the incidence of these tumors decreases to 84% in passive smokers and to 42% in active smokers; and that in the latter cases there is a proportional increase in squamous cell carcinoma and small cell carcinoma[23]. These are similar to our findings.

In these reports, however, there are no consistent results concerning significance or dose response, and there is no unified interpretation at this time.

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Some of the explanations for the inconsistencies are the following: (1) Differences in the living environment, (2) lack of definite information on passive smoking before marriage, (3) differences between women who work outside and those who are self-employed, (4) duration of periods when husband and wife are together, (5) smoking habit of the husband and conditions in the home, (7) mealtime habits, (8) incidence of cancer in the family and (9) age when the cancer developed. The paucity of information on these matters has been pointed out[6,13]. The present study was a survey of the Nara region where most women who were the subjects of the investigation were self-employed. Information was gathered regarding the histologic type of tumor, time of exposure to smoking, and incidence of cancer in the family, and although the number of cases was small, a certain degree of control was exercised. Correa[10] studied the relation of lung cancer to past exposure to passive smoking, and concluded that the effect of smoking by the mother could be seen in male lung cancer patients but not in women lung cancer cases.

Extrinsic and intrinsic factors may interact in carcinogenesis. The leading extrinsic factor in lung cancer is presumably cigarette smoking, while genetic cancer may be an intrinsic factor. We investigated the history of relatives three times removed from the principal, and found that with adenocarcinoma there was a strong indication of association of familial incidence of cancer, while with squamous cell carcinoma and small cell carcinoma, association of familial incidence was seen but not to a significant degree in comparison with controls. The association, however, was observed in 4 out of 5 cases of small cell carcinoma while in squamous cell carcinoma there was more variability. There is need for further study in larger numbers of cases. In another investigation of familial factor, the risk of development of lung cancer when there has been a family incidence was 8-fold over cases without any familial occurrence of lung cancer in Kawasaki City, and 5.9-fold in Tokyo[18]. Aoki[19] also pointed out that the risk of cancer of many organs was 2-3 times higher in families which had cases of cancer than in families without such history.

Tokuhata[21], in a survey of 270 cases of lung cancer, assessed the risk when familial incidence and active smoking were combined, and found the following: Compared with individuals without either factor, the risk for the non-smoker with familial history was 3.96-fold; for the smoker without familial history it was 5.45-fold; and for the smoker with familial history it was 13.64-fold. He stated that when corrected for smoking habit, the risk for those with familial history was increased 2.5-fold, approximately the same level of risk as that of smoking, and claimed that the two factors are synergistic.

In our present study, the findings indicated that compared with controls,

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passive smoking, current or past, increased the risk for lung cancer when familial history was present. When the data were sorted according to histologic type of lung cancer, risk was increased for squamous cell carcinoma and small cell carcinoma when active or passive smoking was combined with familial history, while with adenocarcinoma the influence of familial history was considerable, and the effect of passive smoking in the past was suspected.

Since the number of cases was small and the amount of passive smoking could not be determined so that dose response could not be demonstrated, no definite conclusion could be drawn from the present study, but there was a suggestion that for women in the Nara region, passive smoking is associated with development of lung cancer in women. The effect of passive smoking which has continued to the present time was especially marked, particularly notable in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, the effect of passive smoking in the past was suspected.

Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, was apparent.

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PASSIVE SMOKING IS A RISK FACTOR FOR LUNG CANCER IN NEVER SMOKING WOMEN IN HONG KONG

TAI HING LAM, KAR KEUNG CHENG
Department of Community Medicine, University of Hong Kong, Li Shu Fan Building, 5 Sassoon Road, Hong Kong.

INTRODUCTION

In Hong Kong, lung cancer is the leading cause of death due to malignant neoplasms in both sexes. On a world scale, lung cancer death rates among men are not particularly high in Hong Kong. However, the rates in women are among the highest in the world. Four case control studies have been carried out in Hong Kong to investigate the risk factors for lung cancer in women, particularly smoking and passive smoking. They are reviewed as follows:

I. 1976-1977 STUDY

The first major study on risk factors for lung cancer was a case control study on 208 male and 189 female patients. The controls were 204 male and 189 female hospital orthopaedic patients. Smoking was found to be a major risk factor in males with a relative risk (RR) of 27.51. In females, the RR for smoking was only 3.48. 44.4% of the cases were non-smokers whose tumours were predominantly adenocarcinomas (45.2%).[1]

The role of passive smoking was studied by simply asking the question of "Are you exposed to the tobacco smoke of others at home or at work?" For non-smoking women, 40.5% of the cases and 47.5% of the controls had passive smoking. The RR for passive smoking was 0.75 (P=0.38).[2]

II. 1981-1983 STUDY

In the second case control study, 200 female cases and 200 district female controls matched for age were interviewed in depth using a semi-structured questionnaire. The RR for ever smoking was 2.77. 44.0% of the cases had never smoked.

Among the never-smoked wives, 61.4% of the cases and 51.8% of the controls had smoking husband. The RR for passive smoking due to smoking husband was 1.48 (P=0.16).[3]

III. 1981-1984 STUDY

The third case control study included 163 female cases and 185 female controls from hospital orthopaedic patients. Unlike the previous two studies, only histologically and/or cytologically confirmed cases were included. A standardized questionnaire was used for interviewing. The RR for smoking was 4.12. The proportion of cases who were non-smokers was 46.0%.

The role of passive smoking was studied only on the adenocarcinoma cases. For non-smoking women, 61.7% of the adenocarcinoma cases and

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44.4% of the controls had passive smoking due to smoking husband. The RR for passive smoking was 2.01 (P<0.05). Analysis was also carried out by the site of the tumour. For centrally sited tumour, the RR for passive smoking was 1.61 (P>0.05). For peripheral tumour, the RR was 2.64 (P<0.05).

IV. 1983-1986 STUDY

This was the largest case control study on lung cancer in women in Hong Kong. A standardized structured questionnaire was designed for interviewing. All the cases were confirmed pathologically. They were compared with 445 female healthy neighbourhood controls matched for age. The RR of ever smoking was 3.81.

45.5% of the cases were never smokers. For never smoking women, 57.8% of the cases and 45.4% of the controls had passive smoking due to a smoking husband. The RR for passive smoking was 1.65 (P<0.01, 95% C.I.=1.16, 2.35).

When broken down by cell type, the proportion of never smokers of 62.4% was the highest in adenocarcinoma and it was only in this cell type that the RR for passive smoking was statistically significant (RR=1.87, P<0.01, 95% C.I.=1.23, 2.85). Significant trends for RR with amount smoked daily by husband were observed for all cell types combined and for adenocarcinoma only.

TABLE I

SUMMARY OF RESULTS ON PASSIVE SMOKING AMONG NON-SMOKING WOMEN IN 4 CASE CONTROL STUDIES IN HONG KONG

Study*	Cases/Controls		Total no. of cases & controls	Relative risk	P value
	Passive smoking	No passive smoking			
1976-1977 Chan & Fung, 1983	34/66	50/73	223	0.75	0.38
1981-1983 Koo et al, 1985	54/71	34/66	225	1.48	0.16
1981-1984 Lam WK, 1985	37/64	23/80	204	2.01	0.03
1983-1986 Lam TH et al, 1987	115/152	84/183	534	1.65	0.007
Grand Total	240/353	191/402	1,186	1.43**	0.004

* The study by Lam WK included only adenocarcinoma whereas the other three studies included all cell types.

** Summary relative risk by Mantel Haenszel's method

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SUMMARY OF RESULTS ON PASSIVE SMOKING

Table I shows the summary of results of the above four studies. Apart from the earliest study in which only one simple question was asked about passive smoking, they all showed a RR greater than unity. Statistical significance was reached in the recent two. The Mantel-Haenszel's summary RR was 1.43 ($P<0.01$, 95% C.I.=1.12, 1.83).

In a review of epidemiological and other evidence on passive smoking and lung cancer, Blot and Fraumeni estimated a 30% excess risk[6] while Wald et al calculated a relative risk of 1.35 by pooling the results of ten case control studies and three prospective studies.[7] The summary RR of the four case control studies in Hong Kong is close to these estimates. Because the local prevalence of smoking among women was low (4.1%),[8] the influence by misclassification bias would be much less than in western countries and could not account for the relatively high RR. The results in Hong Kong therefore strongly suggest that passive smoking is a risk factor for lung cancer in never smoking Chinese women.

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Epidemiologic Characteristics and Multiple Risk Factors of Lung Cancer in Taiwan*

CHIEN-JEN CHEN[1,2], HSIN-YING WU[1], YA-CHIEN CHUANG[3], AH-SENG CHANG[2], KUN-TAI LUH[1], HSIO-HSIUNG CHAO[4], KUANG-YAW CHEN[4], SHIN-GON CHEN[5], GI-MING LAI[6], HSIH-HSIN HUANG[7] and HONG-HSIN LEE[5]

[1]*Institute of Public Health, National Taiwan University College, of Medicine, Taipei, Taiwan;*
[2]*Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan;*
[3]*Department of Epidemiology, Pittsburgh University School of Public Health, Pittsburgh, Pennsylania, U.S.A.;*
[4]*Veteran General Hospital, Taipei, Taiwan;*
[5]*Bureau of Public Health, Department of Health, Executive Yuan, Taipei, Taiwan;*
[6]*Chang-Gung Memorial Hospital and Medical College, Taipei, Taiwan;*
[7]*Cathay General Hospital, Taipei, Taiwan*

Abstract. *The specific aim of this study was to examine epidemiologic characteristics and multiple risk factors of lung cancer in Taiwan. The age-adjusted mortality from lung cancer has been increasing since the early 1950s with a constant male-to-female ratio of around 2.0. International comparison of cumulative moratlity from lung cancer showed a much lower male-to-female ratio in Chinese than in other populations. Significantly high moratlity from lung cancer was observed in highly urbanized cities and the endemic area of chronic arsenicism in Taiwan. Significant associations of active and passive cigarette smoking with epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung were observed in a hospital - based case - control study carried out in Taipei metropolitan areas. Alcohol drinking, coffee drinking and various types of indoor air pollution were not related to lung cancer after the cigarette smoking habit was adjusted through a multiple logistic regression analysis.*

Lung cancer is one of the most important cancers in Taiwan where malignant neoplasm has become the leading cause of death since 1982. The mortality from lung cancer ranked the second in both men and women among various cancer sites in Taiwan (1). The annual number of deaths from lung cancer was as high as 2,500-3,000 in the 1980s (2). It has resulted in a significant socioeconomic impact with a work-year loss of 12,500 annually (1).

The one-year survival rate of lung cancer patients was reported as less than 20% in Taiwan (3). The early detection of lung cancer by chest X-ray, sputum cytology and / or fiber optic bronchoscopy remains ineffective and inefficient (3-5). Other screening methods, including tumor marker levels, still need further evaluation (6). Primary prevention and intervention become an important task in the control of the disease. The identification of risk factors for lung cancer is essential for an effective and efficient primary prevention.

Both genetic and environmental risk factors have been related to the development of lung cancer. Risk factors which have been documented include active and passive cigarette smoking, occupational and environmental exposures to arsenic, asbestos, chromium, mustard gas, radon and polyaromatic hydrocarbons, as well as inadequate consumption of dark green vegetables (7-11). Populations in different areas may have different risk factors for lung cancer, and the same risk factors may be of different importance in different populations and / or areas. The study of risk factors in various populations is important not only for the disease control program, but also for the elucidation of its etiological mechanism.

Although epidemiologic characteristics of lung cancer in Taiwan have been described in two previous reports (12, 13), there has never been a case-control study aimed at elucidating possible risk factors for lung cancer in Taiwan. In this report, we updated the analysis of epidemiologic characteristics of lung cancer mortality and incidence, and examined multiple risk factors for the disease based on a hospital - based matched case - control study.

Materials and Methods

Analysis of mortality and incidence rates. The data on lung cancer deaths

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Correspondence to: Prof. Chien-Jen Chen, Black Building Room 209, Columbia University Comprehensive Cancer Center, 650 West 168th Street, New York, New York 10032, USA.

Key Words: Epidemiology, risk factors, lung cancer.

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Table I. *Secular trend of age-adjusted lung cancer mortality rates per 100,000 population from 1954 to 1988 in Taiwan by sex.*

Year	Age-adjusted mortality		Male-to-female
	Male	Female	ratio
1954-1958	3.88	2.07	1.87
1959-1963	6.49	3.53	1.84
1964-1968	10.35	5.84	1.77
1969-1973	13.97	6.68	2.09
1974-1978	16.65	8.29	2.01
1979-1983	21.79	10.42	2.09
1984-1988	24.91	12.22	2.04

from 1954 to 1988 were obtained from the Taiwan Provincial Department of Health which is in charge of the death certification system in Taiwan. Population data for the same period were abstracted from annual demographic statistics (14). As it is mandatory to register any event of birth, death, marriage, employment and education in household registration offices, mortality data are quite complete and accurate in Taiwan. The incidence of lung cancer in Taiwan was derived from annual reports of national cancer registry (15). As the completeness and accuracy of cancre registry has been assessed in Taipei City only, the incidence data analyzed in this report were limited to those of Taipei City. The mortality from lung cancer in 17 selected countries was obtained from the annual vital statistics published by the World Health Organization (16). Incidence rates of lung cancer among Chinese males and females in San Francisco, Los Angeles, Hawaii, Hong Kong and Shanghai were abstracted from the registration data published by the International Agency for Research on Cancer (17).

In the analysis of mortality and incidence, age-sex-specific rates were first calculated for different areas and / or calendar years. The age was stratified into 15 five-year groups from less than 5 to 70 or more. Age-adjusted mortality and incidence rates were calculated using world population in 1976 (17) as the standard population for the study of secular trend, migrant comparison and geographical variation in Taiwan, while cumulative mortality rates over the age range from 0 to 84 years were for international comparison.

Hospital-based matched case-control study. As most patients suspected of having lung cancer are referred to teaching hospitals for confirmatory diagnosis and treatment in Taiwan, we recruited serial patients with lung cancer from four major teaching hospitals in Taipei City. All patients were newly diagnosed and pathologically confirmed. A total of 354 new cases were recruited and 332 (93.8%) agreed to participate in the study. Hospital controls group-matched with case on hospital, age and sex were recruited from ophthalmic patients of study hospitals with a control-to-case ratio of 3:1. Among 664 recruited controls, 635 (95.6%) of them agreed to participate in the study.

A structured questionnaire was used to obtain socio-demographic characteristics and the history of exposure to risk factors including cigarette smoking, alcohol drinking, tea and coffee drinking, as well as indoor air pollution resulting from burning incense and mosquito coils. The consumption frequency, quantity and duration were inquired for habits of cigarette smoking, alcohol drinking, tea drinking and coffee drinking.

In addition to the questions mentioned above, the interview time and interviewer - assessed reliability of the interviewee's response were also included. The average interview time in minutes was 37.4 and 31.5 respectively for cases and hospital controls. There were 9 (2.7%) cases and 18 (2.8%) controls whose responses were rated as unreliable because of poor memory and / or cooperation. In all, there were 323 cases and 617 hospital controls available for the final analysis. With regard to the pathological type of the 323 lung cancer patients, there were 133 (41.2%) affected with epidermoid carcinoma, 47 (14.6%) with small cell carcinoma, 134 (41.5%) with adenocarcinoma, and 9 (2.8%) with other minor pathological types.

In the univariate analysis, the odds ratio and its statistical significance of each risk factor were assessed for three major pathological types of lung cancer. Mantel - Haenszel chiquare test (18) was used to assess the statistical significance of age-sex-adjusted odds ratios for each risk factor. As several risk factors were inter-correlated, multiple logistic regression analysis (19) was used to estimate multivariate - adjusted odds ratios. In the regression analysis, only significant risk factors observed in the univariate analysis were included in the regression equation. BMDP statistical software was used to estimate regression coefficients through the maximum likelihood method (19).

Results

Secular trend. The secular trend of lung cancer mortality from 1954 to 1988 in Taiwan is shown in Table I. The age - adjusted mortality rate of lung cancer increased strikingly during the period for both males and females; it increased significantly from 3.88 per 100,000 in 1954-1958 to 24.91 per 100,000 in 1984-1988 for males, and from 2.07 per 100,000 in 1954-1958 to 12.22 per 100,000 in 1984-1988 for females. The male-to-female ratio of age-adjusted lung cancer mortality remained around 2.0 during the period from 1954 to 1988.

International comparison, migrant difference and geographical variation. The international comparison of lung cancer mortality in Taiwan and 17 selected countries is shown in Table II. Males in Scotland and The Netherlands had the highest mortality from lung cancer, while males in Taiwan and mainland China had the lowest. Females in Hong Kong and Scotland had the highest mortality, while females in the Netherlands and mainland China had the lowest. The cumulative mortality rate of lung cancer in Taiwan ranked as the 17th and 9th, respectively, for males and females. The male-to-female ratio of the cumulative mortality rate of lung cancer varied significantly from greater than 6.0 in the Netherlands, West Germany and Italy to less than 3.0 in Taiwan, China and Hong Kong.

The comparison of age-adjusted incidence rate of lung cancer among Chinese in different areas is shown in Table III. The rate for males was highest in Singapore and lowest in Taipei, while that for females was highest in San Francisco and lowest in Los Angeles. The male-to-female ratio in age-adjusted mortality from lung cancer ranged from 1.33 in Hawaii to 3.43 in Singapore.

There was also a striking geographical variation of lung cancer mortality among 361 townships and precincts in Taiwan. Generally speaking, males and females had similar geographical variation in age-adjusted mortality of lung cancer with a correlation coefficient of 0.54. High lung cancer mortality was observed in highly urbanized cities as well as in the endemic area of chronic arsenicism, while low mortality was observed in rural townships where aboriginals and Hakka Taiwanese reside. There was a significant correlation in the geographical variations of lung cancer with cancers of the liver, pancreas, bladder and kidney in males and females as

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Table II. *Comparison of cumulative mortality from lung cancer in Taiwan and 17 selected countries.*

Rank	Male		Female	
	Country	CMR	Country	CMR
1	Scotland	21.22	Hong Kong	5.95
2	Netherlands	20.04	Scotland	4.40
3	England & Wales	18.61	Singapore	4.37
4	Hong Kong	13.97	England & Wales	3.97
5	Singapore	13.87	USA	3.43
6	Hungary	13.82	Ireland	3.24
7	Austria	13.52	Canada	2.79
8	Canada	13.16	Hungary	2.56
9	USA	13.04	Taiwan	2.52
10	West Germany	12.99	Israel	2.39
11	Australia	12.59	Australia	2.07
12	Italy	11.47	Japan	2.06
13	Ireland	11.05	Austria	2.05
14	Japan	7.38	West Germany	1.56
15	Israel	7.14	Italy	1.48
16	Chile	5.08	Chile	1.45
17	Taiwan	4.98	Netherlands	1.43
18	China	1.95	China	0.93

CMR: Cumulative mortality rates, 0-84 years (percent)

Table III. *Age-adjusted incidence rates per 100,000 population of lung cancer among Chinese in six cities in Asia and USA.*

City	Age-adjusted mortality		Male-to-female
	Male	Female	ratio
Singapore	68.0	19.8	3.43
San Francisco	57.8	25.1	2.30
Hong Kong	55.5	23.4	2.37
Shanghai	51.2	18.1	2.83
Los Angeles	33.8	13.6	2.49
Hawaii	31.4	23.6	1.33
Taipei	27.7	14.4	1.92

Table IV. *Ecological correlation between age-adjusted mortality rates of lung cancer and other cancers in 361 townships and precincts in Taiwan.*

Correlation	Male	Female
Lung *vs.* liver	0.17	0.24
Lung *vs.* pancreas	0.29	0.21
Lung *vs.* bladder	0.35	0.74
Lung *vs.* kidney	0.24	0.66
Lung *vs.* prostate	0.29	–

well as with cancer of the prostate in males, as indicated in Table IV.

Case-control study. Table V shows frequency distributions of age and sex of 133 epidermoid carcinoma, 47 small cell carcinoma and 134 adenocarcinoma patients and of 617 ophthalmic hospital controls. They were all comparable in the distribution of age and sex. The age-sex-adjusted odds ratios for cigarette smoking on the development of various pathological types of lung cancer are shown in Table VI. There was a significant association between cigarette smoking and epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung, with an odds ratio of 6.66, 3.59 and 2.08, respectively. Futhermore, the duration, quantity and inhalation degree of cigarette smoking were all significantly associated with three pathological types of lung cancer in a dose-response relation. Passive smoking was also correlated with the development of epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung with a significant odds ratio of 4.68, 2.55 and 3.04, respectively.

The age-sex-adjusted risk of developing various pathological types of lung cancer for alcohol drinking, tea drinking and coffee drinking are shown in Table VII. Alcohol drinking was significantly associated with epidermoid carcinoma of the lung with an odds ratio of 1.57. Neither small cel carcinoma nor adenocarcinoma was significantly correlated with alcohol drinking. None of the habits of drinking black tea, half-processed tea and green tea was significantly associated with any pathological type of lung cancer. Coffee drinking was found to be associated significantly with epidermoid carcinoma of the lung only.

Table VIII shows associations between various kinds of indoor air pollution and pathological types of lung cancer. Neither burning incense at home nor type of cooking fuels was related to the development of any type of lung cancer. Burning mosquito coils at home was found to be significantly associated with the development of epidermoid carcinoma and adenocarcinoma of the lung, with an odds ratio of 1.81 and 1.70, respectively.

As risk factors significantly associated with various pathological types of lung cancer were inter-correlated, a multiple logistic regression analysis was empolyed to assess multivariate - adjusted odds ratio for various variables. Separate regression analysis was carried out for each pathological type of lung cancer. Only active and passive cigarette smoking were significantly associated with the three pathological types of lung cancer. Alcohol drinking, coffee drinking and burning mosquito coils at home were not significantly associated with any pathological type of lung cancer after cigarette smoking was adjusted.

Discussion

Increasing secular trend and significant geographical variation are two interesting epidemiologic characteristics of lung cancer. This suggests the importance of environmental factors in the determination of the disease. In this study, we observed an increase in lung cancer mortality in Taiwan since the early 1950s. The result is consistent with those observed in most countries (20). The increas in age-adjusted lung cancer mortality in Taiwan may be attributable to improved diagnostic methods, increased consumption of cigarettes,

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Table V. *Age and sex distributions of 133 epidermoid carcinoma, 47 small cell carcinoma, and 134 adnocarcinoma patients and 617 opthalmic hospital controls in metropolitan Taipei areas.*

Variable	Group	Epidermoid carcinoma No. (%)	Small cell carcinoma No. (%)	Adeno-carcinoma No. (%)	Hospital controls No. (%)
Age	< 55	21 (15.8)	17 (36.2)	38 (28.4)	146 (23.7)
	55-64	59 (44.4)	14 (29.8)	50 (37.3)	244 (39.5)
	65 +	53 (39.8)	16 (34.0)	46 (34.3)	227 (36.8)
Sex	Male	111 (83.5)	36 (76.6)	101 (75.4)	488 (79.1)
	Female	22 (16.5)	11 (23.4)	33 (23.4)	129 (20.9)

Table VI. *Age-sex-adjusted odds ratios for cigarette smoking on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Habit	Yes	6.66***	3.59***	2.08***
	No	1.00	1.00	1.00
Duration (year)	41+	8.43***	5.12***	3.79***
	31-40	6.52	4.30	1.60
	21-30	2.76	3.33	1.52
	1-20	1.70	2.16	1.23
	None	1.00	1.00	1.00
Quantity (cig./day)	31+	11.11***	8.09***	3.61***
	21-30	7.61	4.64	2.34
	11-20	7.05	3.48	1.74
	1-10	2.59	2.45	1.21
	None	1.00	1.00	1.00
Inhalation	Deep	7.23***	4.37**	2.21*
	Shallow	3.67	3.57	1.92
	None	1.00	1.00	1.00
Passive smoking	Yes	4.68***	2.55*	3.04***
	No	1.00	1.00	1.00

* $p < 0.05$. ** $p < 0.01$, *** < 0.001 based on Mantel - Haenszel chi-square tests.

Table VII. *Age-sex-adjusted odds ratios for beverage drinking on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Alcohol drinking				
Habit	Yes	1.57*	1.36	1.17
	No	1.00	1.00	1.00
Frequency (days/week)	4+	1.72*	1.90	1.50
	1-3	1.43	0.90	0.98
	None	1.00	1.00	1.00
Tea drinking				
Black tea	Yes	0.20	1.10	0.19
	No	1.00	1.00	1.00
Half-processed tea	Yes	1.52	0.99	0.99
	No	1.00	1.00	1.00
Green tea	Yes	1.48	1.20	1.77
	No	1.00	1.00	1.00
Coffee drinking	Yes	2.10*	1.44	1.25
	No	1.00	1.00	1.00

* $P < 0.05$ based on Mantel - Haenszel chi-square tests

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Table VIII. *Age-sex-adjusted odds ratios for various types of indoor air pollution on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Burning incense	Yes	0.77	1.33	0.99
	No	1.00	1.00	1.00
Burning mosquito coils	Yes	1.81*	1.13	1.70*
	No	1.00	1.00	1.00
Cooking fuels	Wood & coal	0.85	1.08	1.02
	Charcoal, gas & electricity	1.00	1.00	1.00

* $p < 0.05$ based on Mantel - Haenszel chi - square tests.

rapid industrialization and urbanization, and worsened air pollution. International comparison of cumulative mortality from lung cancer revealed a striking difference in the male-to-female ratio among 18 countries studies. The reason for a much lower male-to-female ratio among Chinese in various countries deserves further investigation. As most Chinese women are non-smokers and 60% of female lung cancer patients are affected with adenocarcinoma (12), it seems reasonable to suspect that risk factors other than active cigarette smoking are involved in the development of adnocarcinoma. The striking geographical variation in lung cancer mortality among 361 townships and precincts in Taiwan also suggests the importance of environmental factors. Heavy air pollution resulting from urbanization and industrialization may at least partly contribute to the high mortality from lung cancer in cities. Consumption of high-arsenic artesian well water has been documented to be the major risk factor for lung cancer in the endemic area of chronic arsenicism (21). The significant ecological correlation between mortality rates of lung cancer and pancreas cancer may be explained by the better dignosis of the latter in urbanized areas. However, the similar geographical variation in mortality from cancers of the lung, liver, bladder, kidney and prostate may be attributable to their associations with arsenic exposure from drinking water.

In our case-control study, both active and passive cigarette smoking were significantly associated with the development of three pathological types of lung cancer. Almost all epidemiological studies and animal experiments consistently show a significant association between cigarette smoking and lung cancer (7-9, 22). Both epidermoid carcinoma and small cell carcinoma had a stronger association with active cigarette smoking than adenocarcinoma in this study. This observation is consistent with those reported previously. However, there was no difference in the association with passive cigarette smoking for the three pathological types of lung cancer. Futher investigations are needed to explain such a discrepancy.

Habits of alcohol drinking and coffee drinking were significantly associated with the development of epidermoid carcinoma of the lung in the univariate analysis in this study. However, the association was no longer significant after further adjustment for the effect of cigarette smoking. Indoor air pollution has been documented to cause lung cancer in Yunnan Province of China (10). In this study, an effort was made to assess the effects of various types of indoor air pollution on the development of lung cancer. Although a significant association between lung cancer and burning mosquito coils at home was observed in the univariate analysis, it became not significant after active and passive cigarette smoking were adjusted for. The reduction of cigarette smoking through public education remains the most important task for the primary prevention of lung cancer.

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Dr. G. H. Miller, the author of "The Impact of Passive Smoking: Cancer Deaths among Nonsmoking Women" requested that a revised Abstract be printed to clarify several points.

ABSTRACT

In order to obtain an estimate of the impact of passive smoking on cancer mortality, a retrospective study was conducted examining the cancer mortality of nonsmoking wives with no known or minimal exposure in contrast to nonsmoking wives with moderate to life-time exposure to tobacco smoke. The study was based on the data from 906 deceased nonsmoking women who resided in Erie County, Pennsylvania, who were divided into the following three categories:

1. No known exposure
2. Exposed nonemployed
3. Employed (assumed to be exposed to environmental tobacco smoke in the workplace)

The data were analyzed by the retrospective case-control method using cancer deaths as the cases and non-cancer related deaths as the controls. Also, the data from 401 smoking women were used for comparative purposes of the total percentage of cancer deaths among three groups:

1. Nonsmoking, nonexposed women
2. Combined nonsmoking unemployed and employed exposed women
3. Smoking women

The major finding from the study are

1. Only (2.2%) of the total deaths reported among the nonsmoking women with no known or minimal exposure to tobacco smoke were due to cancer of any site.
2. No cases of lung cancer deaths were reported for the nonexposed, nonsmoking women, and eight lung cancer deaths were reported among the nonsmoking women who were exposed to passive smoking. Also, for this small group of 179 nonsmoking nonexposed women, there were no reported cases of breast cancer, genitourinary or lymphatic cancer.
3. Employed nonsmoking women experienced proportionately more cancer deaths (34.3%) than both nonexposed (2.2%) and exposed nonemployed wives (18.9%). The combined groups of exposed nonsmoking wives (nonemployed and employed) contracted 25.5% cancer deaths.
4. Age-adjusted data showed similar trends.
5. Cancer death rates for women smokers was 35.5% of the total deaths of women smokers.

Public health officials should consider requiring that the workplace be free from tobacco smoke since these data imply that passive smoking has a very detrimental effect upon nonsmokers. Also, smokers should be made aware of the potential damage they inflict on others in their home as well as the workplace.

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The Impact of Passive Smoking: Cancer Deaths among Nonsmoking Women

G.H. Miller, Ph.D., CPC

ABSTRACT

In order to obtain an estimate of the impact of passive smoking on cancer mortality, a retrospective study was conducted examining the cancer mortality of nonsmoking wives with no known or minimal exposure in contrast to nonsmoking wives with moderate (up to 19 years) to lifetime exposure to tobacco smoke. The study was based on the data from 906 deceased nonsmoking women from Erie County, Pennsylvania, who were divided into the following three categories:

1. No known exposure
2. Exposed nonemployed wives
3. Employed wives assumed to be exposed to environmental tobacco smoke in the workplace

The data were analyzed by the retrospective case-control method using cancer deaths as the cases and non-cancer related deaths as the controls. The major findings from the study are

1. Only 2.2% of the deaths reported among the women with no known or minimal exposure to tobacco smoke were due to cancer of any site.
2. No cases of lung cancer were reported for the nonexposed women, and eight lung cancer deaths were reported among the nonsmoking women who were exposed to passive smoking.
3. Employed women experienced proportionately more cancer deaths (35.3%) than both nonexposed (2.2%) and exposed nonemployed wives (25.5%).
4. Age-adjusted data showed similar trends.

Public health officials should consider requiring that the workplace be free from tobacco smoke since these data imply that passive smoking has a very detrimental effect upon nonsmokers both at home and in the workplace.

Key Words: passive smoking, lung cancer, breast cancer.

I. INTRODUCTION

Whether or not passive smoking is detrimental to health has been extensively considered in the last decade. The first reports on the effects of long-term exposure to passive smoking appeared in the late 1970s.[1-3] Prior to that time, it was generally assumed that passive smoking was not of much consequence. However, most health professionals were aware of reports of moderate-to-severe eye irritation as well as allergic reactions to tobacco smoke.[1-3] There were also reports of the serious health consequences observed in animals after exposure to high concentrations of tobacco smoke.[1] In the 1970s, research reports discussed the effect of increased respiratory diseases in children of smoking parents.[2] These were followed by the 1980 Surgeon General's report on the harmful effects of cigarettes on the health of smoking women, including research reporting lower birthweights among children of smoking mothers.[4] Passive smoking has been associated with deleterious effects on the fetus.[5,6]

In 1978[7] and 1979,[8] at the Third World Conference on Smoking and Health, Miller[7,8] proposed a passive smoking classification based on three different exposure levels: (1) short-term — a few minutes to a few hours; (2) moderate-term — less than 2 decades; and (3) long-term — 2 decades to a lifetime. He suggested that studying the consequences of long-term exposure provided the best opportunity for observing the effects, if any, of passive smoking. He reported a 4-year earlier average-age-at-death of nonsmoking women exposed to their husbands' cigarette smoke compared with nonsmoking, nonexposed women.

White and Froeb[9] in 1979 reported severe lung dysfunction following long-term exposure to tobacco smoke. Hirayama,[10] Tricopolous et al.,[11] and and Correa et al.[12] noted a two- to threefold increase in lung cancer in exposed wives when compared to nonexposed wives. Gillis et al.[13] and Schmidt et al.[14] have also shown that passive smoking is detrimental to the health of the nonsmoker. Miller,[15] Sandler et al.,[16] and Repace and Lowrey[17] each showed a two- to threefold increase in total cancer deaths following long-term exposure to passive smoking. Garfinkel et al.,[18] who had previously found no statistically significant evidence of the detrimental effects of passive smoking, now reports a two- to threefold increase in lung cancer.[19] Wald et al.[20] and Pershagen et al.[21] most recently have provided support for the hypothesis that passive smoking increases lung cancer incidence, largely among spouses. Two reports provide a detailed review of the research on passive smoking, noting its detrimental effects: the Surgeon General[22] recommended a smoke-free environment, and the National Academy of Sciences[23] recommended no smoking in the home environment of children.

In order to obtain additional information on the effects of passive smoking, this study compared different levels of environmental tobacco smoke exposure of married nonsmoking

G.H. Miller, Ph.D., CPC, Studies on Smoking, Inc., 125 High Street, Edinboro, PA 16412.

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women with cause of death. The causes of death included in the study were the usual causes of death such as cardiovascular, cancer, and respiratory diseases but excluded traumatic deaths such as accidents, suicides, and homicides. Men were not included in this study since so many men are exposed to environmental tobacco smoke in the workplace.

II. MATERIALS AND METHODS

A. The Population

The population of Erie County, which includes Erie, the third largest city in Pennsylvania, was 263,654 in 1970. It is primarily a middle income population (the average family income for 1970 was listed as $9,380) with a low migration rate of 7% for the 1950 to 1970 time period as reported by the Pennsylvania Department of Commerce.

B. Methodology

The Northwestern Pennsylvania Study on Smoking and Health (NPSSH) began to gather data in 1973 on the smoking habits of deceased male and female residents in Erie County by interviewing the decedents' next of kin. Death notices for the years 1972 through 1982 were obtained from the local newspaper, which lists the names of approximately 95% of deceased Erie County residents along with information on surviving relatives.

Telephone numbers of one to three surviving relatives were obtained for approximately 85% of the death notices reported in the newspaper. Deaths from accidents, suicides, congenital anomalies, and persons younger than 30 years of age were not included because an age bias is introduced when those classified in these categories have their lives curtailed and therefore would not provide an accurate estimate of the age at which cancer actually occurs for the passive smoking-exposed women. Because of the reduced life expectancy, the inclusion of accidents and suicides would lower the incidence of cancer since those in the lower age cohorts might have contracted some type of cancer had they lived long enough. These individuals comprised about 10% of the total deaths.

A questionnaire designed for telephone interviews was constructed with the assistance of the local branches of the American Cancer Society, the American Heart Association, the American Lung Association, and by smoking and health experts in the Pennsylvania Department of Health. A more detailed description of this questionnaire has been published.[15]

Interviewers explained the purpose of the study to the identified surviving relatives and solicited their cooperation. Information was collected from them on each decedent's cause of death, age, occupation (including information on whether or not the wife worked outside the home), exposure to known sources of pollution (including environmental tobacco smoke), smoking history, and whether or not the spouse and parents smoked. The interviews were conducted by the director of the study and by interviewers trained by him.

The questionnaire was revised in 1975, and additional items were included to obtain more complete information on a spouse's smoking habits such as type and quantity of tobacco used, details on smoking cessation, the age at the time of death and the cause of death, the current age if living, the year or decade of death if deceased. Information on whether any other members of the household smoked was also added.

Detailed data on passive smoking from the revised questionnaire were gathered on the deceased from 23 months in the years 1975, 1976, 1979, and 1980; these were the only data considered in this study. Due to logistical problems, the interviews for deaths occurring in other months were not completed at that time. The total number of deaths among residents of Erie County for these 4 years (Pennsylvania Department of Health) was 10,131 (5478 men and 4653 women). Among the 3538 relatives contacted, 3361 (95%) provided information on 1863 men and 1498 women. Of the 1498 deceased women for whom information was obtained, smoking exposure histories were available for 1423 — 906 nonsmoking wives, who are the subjects considered in this paper, plus data on 401 smokers. Of the remaining 116 deceased nonsmoking women, 63 never married and 53 did not have sufficient information on passive smoking to include in this study. For example, the statement that a husband was a smoker was not considered sufficient evidence if details on amount and type of tobacco use were unavailable, resulting in the exclusion of the wife from this study. These data are summarized in Table I.

In this study, a nonsmoker was defined as a person who had smoked fewer than 20 packs of cigarettes during his or her lifetime. A nonsmoking, nonexposed wife was one who had no known reported exposure to tobacco smoke from any source or minimal exposure (only occasional exposure to pipe, cigar, or cigarette smoke). A nonemployed exposed wife was one who was exposed to cigarette smoke by a family member

Table I
Total Deaths from All Causes, Total Cancer Deaths, and Number of Interviews from the Erie County Population Data Base for the Years 1975, 1976, 1979, and 1980

	All causes	All cancer	Total interviews	Interviews passive smoking	Interviews used in study
Men	5,478	1,116	1,863	1,793	
Women	4,653	995	1,498	1,423	906*
Total	10,131	2,111	3,361	3,216	

* This figure includes only nonsmoking women with detailed information on passive smoking exposure. It excludes 401 smoking wives and 116 who were never married, single, or of uncertain passive smoking status.

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(husband, children, or relatives) or a nonfamily member, or had reported long-term exposure to smoky rooms in non-employed activities outside the home. An employed wife was identified by a surviving relative as a person engaged in an occupation outside the home for more than 3 years.

In order to insure a clearly defined category for nonexposure, all those who may have had any potential moderate-to-heavy exposure were eliminated from this category. Therefore, those not included in the nonexposed spouse category, in addition to the 401 smoking women, were (1) women who were married at any time to a smoker; (2) women exposed by family or friends or exposed in nonemployed activities; (3) all nonsmoking employed women.

Although some nonexposed individuals might have been eliminated by these definitions, the nonexposed category as defined here is as free as possible from the inclusion of those who may have been exposed for longer periods of time. The nonsmoking wives were categorized in the following three groups based upon the information reported in the telephone interviews with relatives:

1. NX — nonexposed (no known or only minimally exposed) wives
2. ENE — exposed nonemployed wives
3. EW — Employed wives who were assumed to have some exposure at work

The data were analyzed using the retrospective case control techniques described by Fleiss.[24] The "cases" were defined as deaths (among nonsmoking wives) due to cancer of any kind while the "controls" were noncancer deaths among nonsmoking wives. These deaths included cardiovascular, respiratory, kidney, and other noncancer diseases, but excluded traumatic deaths such as accidents and suicides.

The classification of the cause of death as recorded on the death certificate was provided by the ICD (International Classification of Diseases) codes listed on computer printouts provided by the Pennsylvania Department of Health. The causes of death reported by the next of kin were not used since the ICD codes are considered more accurate. However, the information provided by the surviving relatives was very close to the ICD codes when comparison was made between the next of kin's report of the cause of death given during the interview and the ICD (Death Certificate) disease designation. Details on these data will be reported separately.

In order to be sure that all those classified as having no known exposure to carcinogenic compounds of tobacco smoke were classified correctly, very close relatives of the deceased were located and interviewed if the first interviewee was not a close relative, or close relatives were interviewed again to obtain greater accuracy in the classification of the nonexposed. During this interviewing, it was discovered that two women classified as nonexposed who died of breast cancer were actually exposed to cigarette smoke by their husbands and children. This reduced the total cases of cancer among nonexposed women from six to four.

Because of the small numbers with different types of cancer, only the major cancer categories were considered as noted in the standard International Classification of Diseases: Oral (140–149), Digestive tract (150–159), Respiratory (160–163), Breast (174), Genitourinary (180–189), Lymphatic (200–209), and All Other Cancer Sites.

Although specific details on cancer deaths due to smoking are not considered in the present study, a comparison was made with the nonexposed (NX), the exposed nonsmokers (ENE and EW), and smokers (employed and nonemployed) to provide comparisons between the nonexposed, exposed nonsmokers, and smokers.

In order to check for potential bias due to age, the data were age adjusted for all cancer causes and for the major categories of cancer: oral, breast, lung, respiratory, genitourinary, and lymphatic.

III. RESULTS

Analysis of the data in the two by three contingency table [(Table II—two categories: cancer cases and noncancer cases compared with the three categories: NX (nonexposed wives), ENE (exposed nonemployed wives), EW (employed wives)]

Table II
Deaths among Nonexposed and Exposed Nonsmoking Wives

	Cancer deaths	Noncancer deaths	Total deaths	Percent cancer deaths
Nonexposed,				
(1) nonemployed	4	175	179	2.2
Exposed,				
(2) nonemployed	78	334	412	18.9
(3) Employed	108	207	315	34.3
Total	190	716	906	21.0

Chi square for above 3 by 2 matrix (2 DF) = 72.64

Chi square evaluations for 2 by 2 comparisons (1 DF)

		Odds ratio	Chi square
(1) vs. (2)	(Nonexposed vs exposed nonemployed wives)	10.2	29.0
(1) vs. (3)	(Nonexposed vs. employed wives)	22.8	66.9
(2) vs. (3)	(Exposed nonemployed wives vs. employed wives)	2.2	22.3
(1) vs. [(2) + (3)]	(Nonexposed vs. exposed nonemployed and employed wives)	15.0	47.2

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showed a Chi Square value of 72.64 with 2 degrees of freedom ($p \ll 0.01$).

Table II also shows four different comparisons of the three subgroups: (1) nonexposed wives (NX) with exposed nonemployed wives (ENE); (2) nonexposed wives (NX) with employed wives (EW); (3) exposed nonemployed wives (ENE) with employed wives (EW); and (4) nonexposed wives (NX) compared with the combination of exposed nonemployed wives (ENE) and employed wives (EW). The data from Table II show that exposure to environmental tobacco smoke is associated with increased cancer mortality, resulting in an odds ratio of 10.2 when comparing nonexposed wives with nonemployed wives; an odds ratio of 22.8 when comparing nonexposed wives with employed wives; an odds ratio of 2.2 when comparing exposed nonemployed wives with employed wives; and an odds ratio of 15.0 when comparing nonexposed wives with exposed nonemployed wives and employed wives.

Proportionally far fewer nonsmoking nonexposed wives died of cancer than the exposed wives. The comparison of the exposed nonemployed wives with employed wives also showed highly significant excesses in cancer mortality among the employed women.

Table III shows the mortality from cancer by primary site for the three different exposure groups (NX — nonexposed wives; ENE — exposed nonemployed wives, and EW — employed wives) for the major categories of cancer (oral, digestive tract, breast, genitourinary, lymphatic, and other sites). There were no reported deaths from oral, lung, breast, genitourinary, and lymphatic cancer among the 179 deaths within the nonexposed women. One death from digestive cancer and three deaths from "other" cancers were reported for the nonexposed. Eight deaths due to lung cancer were reported among the 727 deaths of exposed (nonemployed and employed) nonsmoking wives.

Figure 1 shows the percentage of deaths due to cancer among nonexposed wives, exposed wives (both nonemployed and employed), and smoking wives. Although smoking wives are not considered in detail in the present study, the preliminary data are provided here for comparative purposes:

1. Nonexposed nonemployed wives — 2.2%
2. Exposed (employed and nonemployed) wives — 25.5%
3. Smoking wives (employed and nonemployed) — 35.3%

In addition, the data for cancer deaths were age adjusted by the standard age-adjusting methods. The cancer deaths were adjusted to cause distribution of all female decedents in the years considered in this study (1975, 1976, 1979, 1980) from Erie County based on the data from the Pennsylvania Department of Vital Statistics. The results of the expected and observed were analyzed by the two-way probability based on the Poisson distribution and are reported in Table IV. The Poisson distribution was used since the nonexposed group had so few cases. Table IV shows the results after age adjusting for all cancer cases, digestive cancer, and the results for the combination of oral, lung, breast, genitourinary, and lymphatic cancers which appear to be associated with effects of passive smoking.

IV. DISCUSSION

While many epidemiologists prefer to conduct prospective studies, the retrospective study has the advantage of allowing one to obtain estimates in a short time. Thus, this type of a research provides mortality data related to information on the smoking habits of the deceased.

Because nonsmoking women may be exposed to numerous sources of tobacco smoke, this study tried to eliminate as many of the sources of tobacco smoke exposure as possible in order to more accurately classify women into a "pure" nonexposed category. It is probable that persons in this "pure" category have had some small exposures to tobacco smoke during their lives, because minimal exposure is difficult to avoid.

The present study was designed to obtain smoking history data on all nonsmoking wives who died during the specified years. While it is difficult, if not impossible, to obtain data on all members of a population, there is little reason to believe that the 23-months' sampling of the 4-year population was

Table III
Major Types of Cancer for Nonexposed and Exposed Nonsmoking Wives

Type of cancer	Oral	Digestive tract	Respiratory	Breast	Genitourinary	Lymphatic	Other sites	Total	Average age at death
ICD classification	140—149	150—159	160—163	174	179—185	200—209			
NX	0	1	0	0	0	0	3	4	84.5
ENE	0	28	3	14	9	8	16	78	71.1
EW	0	38	5	25	14	10	16	108	67.8
Total	0	67	8	39	23	18	35	190	

Note: ICD: International classification of disease; NX: nonexposed wives; ENE: exposed nonemployed wives; EW: employed wives; Total: exposed and nonexposed wives.

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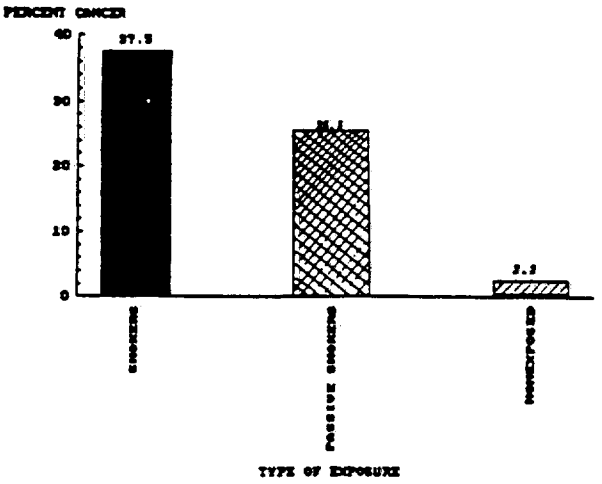

FIGURE 1. A comparison of mortality rates of smokers, passive smokers, and the nonexposed.

Table IV
Analysis Using Age-Adjusted Values for Cancer Sites (All Cancer, Digestive, and Passive Smoking-Associated Cancer) for the Three Major Nonsmoking Groups

Disease	Group	EXP	OBS	Probability
All cancer				
	Nonexposed	24.0	4	0.00002
	Exposed nonemployed	73.1	78	NS
	Exposed employed	70.6	108	0.001
Digestive Cancer				
	Nonexposed	9.3	1	0.002
	Exposed nonemployed	24.2	28	NS
	Exposed employed	20.4	38	0.01
Passive smoking-associated cancer				
	Nonexposed	9.2	0	0.0002
	Exposed nonemployed	35.7	34	NS
	Exposed employed	38.9	54	0.1

biased in the types of cancer deaths that would have occurred during these years. Analysis of the data of previous nonrespondents showed the same basic distribution of cancer deaths as the analysis of original respondents. Therefore, the data from this population study are likely to be representive of the actual population.

These data provide evidence that nonsmoking women exposed to cigarette smoke (generated by smoking husbands, other smokers in the household, or in outside activities) has a higher probability of dying of cancer of all kinds than women who have no known exposure, i.e., cancer mortality in nonsmoking Erie County wives with no known exposure to tobacco smoke is very low — only 2.2% vs. 25.5% for exposed women and 35.3% for smoking wives (Figure 1).

The data imply that the absence of passive smoking could lead to even lower rates of cancer mortality for the total population. Thus, these data indicate that passive smoking is very detrimental to the health of the nonsmoker.

The total proportion of deaths due to cancer for the 401 smoking and 906 nonsmoking wives in this study is 23.9%. This result is close to the proportion of deaths due to cancer for women in Erie County (21.8%) for the years considered in the study as reported in the Pennsylvania Department of Health — Division of Vital Statistics. This agreement suggests that the data are representative of the total population.

The observation that the nonsmoking employed wives had an odds ratio of 2.2 of dying of cancer when compared with exposed nonemployed wives suggests that workplace exposures may involve important hazards in addition to, or apart from, tobacco smoke. Over 80% of the employed wives in this study were either office workers, in sales occupations, teachers, or nurses, who (aside from the nurses) should have had little contact with carcinogenic agents other than tobacco smoke. The doubling of the rates of cancer for employed women compared with nonemployed women are in agreement with the data of Repace and Lowry[25] and the estimates made by Wells.[26] It may be that work place passive smoking exposure is higher than at home. Another possible explanation is that the employed wives may receive additional tobacco smoke exposure from smokers at home such as from their spouse, i.e., their husbands may be more likely to be smokers or heavy smokers.

Also of interest is the observation that only 8 deaths due to lung cancer were reported among the total of 727 passively exposed nonsmoking wives. Thus passive smoking does not result in large numbers of lung cancer cases when compared to active smoking. This difference is in agreement with the results of several studies by Hirayama.[10] Tricopoulos et al.,[11] and Correa et al.[12] showing two- to threefold increases in lung cancer for exposed vs. nonexposed wives and a much larger increase for smokers. In addition, a study by Miller[27] on the Amish — a nearly completely nonsmoking population — showed no lung cancer cases among either male and female nonsmokers for the Lancaster County, Pennsylvania, Amish for the 1970 to 1980 decade.

There were no reported deaths from lung cancer, breast cancer, genitourinary, or lymphatic cancer among wives with no known exposure to tobacco smoke among the total of 179 deaths in the nonexposed category. This contrasts with the distribution of cancer mortality for women in the general population of Erie County for the years under consideration: lung cancer — 12.7%; breast cancer — 20.7%, and lym-

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phatic cancer — 8.7%. These Erie County percentages of cancer causes by site are close to the national averages. Thus it appears that the types of cancer reported in the nonexposed group are very different from the types of cancer reported for both passive smoking and active smoking groups. While it has been shown that passive smoking causes some lung cancer cases, the amount is small compared with that of those who smoke.

Whether or not breast cancer is caused by active or passive smoking has become a controversial issue. Previously, it was thought that breast cancer was not active-smoking related. For example, no editions of the U.S. Surgeon General's Reports from 1964 to 1989 show any subsections devoted to active smoking and breast cancer. However, the Bibliography of Smoking and Health and Index Medicus provides reports of many studies on the topic of smoking and breast cancer. The most recent studies appear to be equally divided between those concluding that there is no overall positive association with active smoking and breast cancer[28-31] and those that conclude a positive and, in some cases, a significant association between active smoking and breast cancer.[32-35]

It has been only recently that studies have taken into account the potential effect of passive smoking and its possible association with breast cancer. Two of the most recent studies were completed by Sandler et al.[36] and Horton.[37] Two other major cancer categories have been reported as being associated with passive smoking exposure — lymphatic cancer, by Wells;[26] and cervical cancer, by Slattery et al.[38] The data from the present study agree with the studies noted above.

The possibility of passive smoking being associated with cancer sites was also verified by the highly significant values obtained after age adjusting for total cancer, digestive cancer, and the combined passive smoking-related cancer sites (refer to Table IV).

Since many studies during this decade have come to the conclusion that breast cancer is not smoking related, this new data might appear to be questionable. However, past studies failed to allow for such passive smoking categories as employed women and others smoking in the household. Therefore, the results of the NPSSH study should provide a more accurate estimate of passive smoking exposure.

A recent article by Bailar and Smith,[39] pointing to the continued increase in cancer mortality despite our apparent gains in early identification, as well as improvements in the treatment of cancer, shows that cancer is still increasing in the population. It may be that the cumulative long-term effects of both passive smoking and active smoking are continuing to have an impact on this increased cancer mortality. These issues have important implications for both the home and the workplace.

More research is needed to validate these observations. New studies require:

1. Better estimates of exposure to passive smoking. The nonsmoking category should exclude employed women, women exposed at home by individuals other than their spouse, and long-term exposure in outside nonemployed activities, as well as exposure at home by their spouse.
2. Long-term exposure information — preferably a minimum of 3 decades-to-lifetime exposure. Studies involving a few weeks or months or even a few years of exposure are inappropriate for an analysis of the true long-term impact of passive smoking.
3. Large enough samples to provide valid data.

For comparative purposes with the results of this study, the author would like to see more population studies instead of nonrandom or nonpopulation based samples in order to overcome the biases that are inherent in these types of sample designs.

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